COUNTWAY LIBRARY
HC 3IIQ Y

THE FRANCIS A. COUNTWAY LIBRARY OF MEDICINE
HARVARD MEDICAL LIBRARY-BOSTON MEDICAL LIBRARY

Digitized by the Internet Archive
in 2015

https://archive.org/details/rhodeislandmedic7516rhod

RHODE ISLAND MEDICINE

January 1992

Volume 75, Number 1

75th ANNIVERSARY ISSUE

Breast Cancer Screening in Rhode Island

Help reduce breast cancer deaths by at least ***25*** percent . . .

Refer your female patients for regular screening mammograms

Twelve major medical organizations recommend that asymptomatic women ages 40-49 should have a screening mammogram every 1-2 years, and a physician's examination every year. Asymptomatic women 50 and older should have a mammogram and a physician's exam every year.

Scientists estimate that if women followed these guidelines, breast cancer deaths would **decline** by at least ***25*** percent.

AMERICAN CANCER SOCIETY®

1599 Clifton Rd., N.E.
Atlanta, GA 30329

acr

1891 Preston White Drive
Reston, VA 22091

RHODE ISLAND MEDICINE

Volume 75, Number 1 January 1992

EDITORIAL STAFF

Stanley M. Aronson, MD
Editor-in-Chief

Kimberly A. Poulton
Managing Editor

Hugo Taussig, MD
Book Review Editor

Seebert J. Goldowsky, MD
Editor-in-Chief Emeritus

EDITORIAL BOARD

*Edward R. Feller, MD
Chairman

*Joseph Amaral, MD

*Stanley M. Aronson, MD

Edward M. Beiser, PhD, JD

Paul Calabresi, MD

*Richard A. Carleton, MD

Margaret Cololan, MSJ

*James P. Crowley, MD

*Peter A. Hollmann, MD

*Margaret A. Neill, MD

*Fred J. Schiffman, MD

William J. Waters, Jr., PhD

*Member of Publications Committee

OFFICERS

Kathleen C. Hittner, MD
President

Robert E. Baute, MD
President-Elect

A. Robert Buonanno, MD
Secretary

Frances P. Conklin, MD
Treasurer

Richard Wong, MD
Immediate Past President

DISTRICT AND COUNTY PRESIDENTS

Fred Vohr, MD
Bristol County Medical Society

Joseph Salvatore, MD
Kent County Medical Society

Orest Zaklynsky, MD
Newport County Medical Society

David P. Carter, MD
Pawtucket Medical Association

James P. Crowley, MD
Providence Medical Association

Joseph R. Dotolo, MD
Washington County Medical Society

Patrick R. Levesque, MD
Woonsocket District Medical Society

TABLE OF CONTENTS

COMMENTARIES

3 An Anniversary – and a New Name

Breast Cancer Screening–A Window of Opportunity
Barbara A. DeBuono, MD, MPH

Epidemiological Characteristics of Breast Cancer

The Language of Epidemiology (VII): Screening Tests
Edward R. Feller, MD

The Father of All Scientific Journals

CONTRIBUTIONS *Guest Editor–Barbara A. DeBuono, MD, MPH*

9 **Evaluating a Mass Media Campaign to Promote Screening Mammography**
John P. Fulton, PhD
Judith P. Feldman, MD, MPH
Edward F. Donnelly, RN, MPH
Jay S. Buechner, PhD
Dolores DiOrio, MEd
Barbara A. DeBuono, MD, MPH
Robert A. Smith, PhD
H. Denman Scott, MD, MPH

16 **Work-up of the Abnormal Mammogram for Palpable and Nonpalpable Breast Masses**
Barbara Schepps, MD, FACR
Patricia K. Spencer, MD
Francis H. Scola, MD, FACR
William Thompson, MD, FACS

21 **Breast Cancer Management in the Nineteen Nineties**
Francis J. Cummings, MD
Arvin S. Glicksman, MD
Harold J. Wanebo, MD

37 **The Differential Diagnosis of Premenstrual Syndrome**
Marguerite Vigliani, MD, FACOG

49 **In the Beginning**
Kimberly A. Poulton
Stanley M. Aronson, MD

COLUMNS

32 HEALTH BY NUMBERS
Breast Cancer Screening among Low-Income Hispanic Women in Rhode Island

55 THE RHODE ISLAND MEDICAL JOURNAL HERITAGE

60 NECROLOGY 1991

Cover: A montage of RHODE ISLAND MEDICAL JOURNAL covers spanning its 75 years of publication.

Rhode Island Medicine is owned and published monthly by the Rhode Island Medical Society, 106 Francis Street, Providence, Rhode Island 02903, Ph 401-331-3207. Single copies $2.00 — Subscriptions $20.00 per year (members of the Rhode Island Medical Society — $5.00 annually). Published articles represent opinions of the authors and do not necessarily reflect the official policy of the Rhode Island Medical Society unless clearly specified. Advertisements do not imply sponsorship or endorsement by the Rhode Island Medical Society. Second class postage paid at Providence, Rhode Island. ISSN 0363-7913 POSTMASTER: Send address changes to RHODE ISLAND MEDICINE, 106 Francis Street, Providence, RI 02903. National Advertising Bureau: State Medical Journal Advertising Bureau, Inc., 711 South Blvd., Oak Park, Illinois 60302. Phone 708-383-8800.

QUESTION:

WHAT ARE THE THREE MOST IMPORTANT THINGS TO CONSIDER WHEN CHOOSING AN INSURANCE AGENCY?

ANSWER:

EXPERIENCE, EXPERIENCE, EXPERIENCE

INSURANCE SINCE 1879

STARKWEATHER & SHEPLEY INC. - (401) 421-6900

Morton Smith, Inc. - (401) 861-6800

155 South Main Street
Providence, Rhode Island 02903

COMMENTARIES

An Anniversary – and A New Name

The first issue of the *Journal*, as a statewide periodical, appeared in January, 1917. The current issue thus marks the seventy-fifth anniversary of the Rhode Island Medical Society's uninterrupted monthly publication. There have been 900 consecutive issues printed and distributed under the name, *Rhode Island Medical Journal.* Both the Publications Committee of the Society and the Editors now agree that a shorter, more succinct title of the publication is needed and concluded that this anniversary issue is the appropriate time for the transition. Accordingly, our publication is now called *Rhode Island Medicine.*

During the past year our publication has increased its size to about 51 pages per issue. Of greater importance, however, is the substantially greater involvement of Rhode Island physicians in its contents. During 1991, for example, 187 different physicians authored or coauthored papers, abstracts or commentaries for our critical inspection; and nine colleagues guest edited various issues during the prior year. The *Rhode Island Medical Journal* has become the literary and scientific voice of the practicing physicians of this state. *Rhode Island Medicine* will continue to seek and publish the thoughts and views of Rhode Island's medical community.

The Editors
The Publications Committee.

Breast Cancer Screening– A Window of Opportunity

The benefits of breast cancer screening are well known.[1-3] Universal screening of eligible women would save between 10,000 and 15,000 lives a year in the US alone. With this goal in mind, eleven national organizations recently issued consensus recommendations for screening: breast exams every year for women ages 40 and over, screening mammograms every year for women ages 50 and over, and screening mammograms every one or two years for women ages 40-49. Despite this consensus and its attendant publicity, however, rates of utilization remain low. In Rhode Island, for example, where resources have been committed to increase utilization, fewer than 50% of eligible women ages 40 and over are screened according to national guidelines.[4]

Several reasons account for the underutilization of breast cancer screening in this country. First, the use of mammography is strongly influenced by provider recommendations. In a recent Rhode Island survey, 57% of women ages 40 and over reported having ever received a provider's recommendation for screening mammography.[4] Second, the cost of mammography limits its use by women of low income. Medicare now covers screening mammography, as do many private insurers. In some states such as Rhode Island, Medicaid covers this test. Still, there is a void for the uninsured woman. Third, the use of mammography is inhibited by women's beliefs about the physical discomfort of the procedure, radiation exposure, and false test results. Some providers, who neither understand nor appreciate the true value of the test, may support and perpetuate these beliefs.

Mammography's ability to uncover early malignancy provides a "window of opportunity" for cure and lessened morbidity. Yet many women, even those with health insurance and few inhibitions about screening, are reluctant to pursue mammography without explicit recommendations from primary care providers. Why do so few women exert independent control over this aspect of their health care?

Two recent articles in the *New England Journal of Medicine* speak to this question. Both discuss gender differences in the management of coronary artery disease. One study found that men were more likely than women to undergo coronary angiography and revascularization procedures during hospitalization for known or suspected coronary heart disease.[5] The other study found that men were more likely than women to be referred for cardiac catheterization and coronary bypass surgery during hospitalization for myocardial infarction, even though women reported greater disability from anginal symptoms.[6] This phenomenon was attributed to fallacious beliefs commonly held by providers: "that angina is a benign symptom in women" and "that stress testing is not accurate for the diagnosis of coronary artery disease in women." In short, the women in these two studies were dependent upon providers' recommendations for

testing and treatment. Many of these recommendations were based on unsubstantiated beliefs about the seriousness of the symptom, the need for screening or the accuracy of the procedure. Why? Because most studies of coronary artery disease have excluded women. The problem is not unique to heart disease research, however. Despite emerging gender differences in disease progression, drug effects, and access to care, women subjects are used infrequently.

Commenting on the articles in the *New England Journal of Medicine*, Dr Bernadine Healy, Director of the National Institutes of Health, observed the "Yentl syndrome" at work: "once a woman showed that she was just like a man by having severe coronary artery disease or a myocardial infarction, she was treated as a man would be."[7] But why must women be Yentls before they receive appropriate care? And what happens with a disease like breast cancer in which 99% of the cases are women? The answer lies in improving awareness of women's health care needs for screening, and treatment among both providers and women themselves. Public health agencies, physicians and researchers should join together in improving access to screening, treatment, and research. Women, in turn, must participate in such programs. They can serve themselves and the medical community as a laboratory for advances in the early detection and treatment of puzzling diseases such as HIV disease, breast cancer, coronary artery disease, and mental illness. In short, women must become **full** partners in their own health care.

To facilitate this process, the Rhode Island Department of Health established its Breast Cancer Screening Program in 1987. The program provides low-cost screening mammograms to asymptomatic women ages 40 and over, working with physicians in the community to promote screening and assure follow-up, but allowing women to refer *themselves* for mammography. Over 5000 women have used it since 1987, many of them first-time users. More importantly, program publicity has increased women's awareness of breast cancer screening, contributing to thousands of first-time screenings outside the program. This model, in which women and providers both play strong roles, might also benefit women who suffer from HIV infection, coronary artery disease, and mental illness.

Gender gaps in health care research and delivery are inexcusable. Working together, public health agencies, physicians, researchers, and *women themselves* must strive to close them. Here in Rhode Island, the Breast Cancer Screening Program is designed to do just that. We must make it work. It is a "window of opportunity" women cannot afford to pass up.

Barbara A. DeBuono, MD, MPH

RHODE ISLAND BREAST CANCER SCREENING PROGRAM

* *Administered by Rhode Island Department of Health*
* *Women, 40 years of age and older are eligible for reduced cost ($50) screening mammography*
* *Low Dose Mammography*
* *Fee for mammography is covered by most health insurers*
* *Thirty-eight (38) radiology sites around the state are participating*
* *Call RI Department of Health at 277-3442 to make an appointment or for more information.*

References

1. Baker, LH. Breast Cancer Detection Demonstration Project: five year summary report. CA 32:194-230 (1982).
2. Tabar L, Fagerberg CJG, Gad A et al. Reduction in mortality from breast cancer after mass screening with mammography: randomized trial from the Breast Cancer Screening Working Group of the Swedish National Board of Health and Welfare. Lancet 1:829-32 (1985).
3. Chu KC, Smart CR, Tarone Re. Analysis of Breast cancer mortality and stage distribution by age for the Health Insurance Plan Clinical trial. JNCI 80:1125-32 (1988).
4. Buechner JS, Fulton JP, Feldman JP, DeBuono BA. Trends in Breast Cancer Screening–Rhode Island, 1987-1989. MMWR 38 (33):569-571,(1989).
5. Ayanian JZ, Epstein AM,. Differences in the use of procedures between women and men hospitalized for coronary heart disease. NEJM 325(4):221-225 (1991).
6. Steingart RM, Packer M, Hamm P, Coqlianese ME et al. Sex differences in the Management of Coronary artery Disease. NEJM 325(4):226-230 (1991).
7. Healy B. The Yentl Syndrome. NEJM 325(4):274-275 (1991).

Epidemiologic Characteristics of Breast Cancer

Breast cancer is now a major public health threat. Its incidence rate in the United States has increased each year during the past three decades and is approaching 89 new cases per 100,000 females per year. During the past decade in Rhode Island, an estimated 7,000 new cases of breast cancer have been identified with about 3,000 deaths.

Breast cancer is not randomly distributed. The incidence rate is particularly high in countries such as the United States, Switzerland and Scandinavia and quite low in Japan and Africa. In Israel, which has a comprehensive cancer reporting system, the breast cancer rate is highest in European-born Jews (62 per 100,000), intermediate in Jews born in Asia or Africa (34 per 100,000) and lowest in the Israeli Arabs (11 per 100,000). Studies in Japanese women also sug-

gest that environmental rather than genetic factors may cause these statistical disparities. The breast cancer rate for Japanese women born in Japan is about 13 per 100,000; with first generation Hawaiian Japanese it is about 36 per 100,000; and with second generation Hawaiian Japanese, 57 per 100,000, closely approximating the non-Asian Hawaiian rate of 66 per 100,000.

What non-genetic, non-ethnic risk factors have been suggested? The total dietary fat intake correlated well with the rates of breast cancer. Where dietary fat intake is low (eg, Japan, Chile, Senegal) the rates of breast cancer are low. And where fat intake is intermediate or high, the breast cancer rates are either intermediate or high. Amongst American populations observing a vegetarian diet (eg, Seventh Day Adventists) the rate of breast cancer remains low. Whether the fat intake *per se* is the carcinogenic force remains quite problematic. Diet may only be surrogate for some other, less obvious exogenous factor. Women who are college graduates, for example, have a strikingly higher rate of breast cancer than those who have not completed high school. Indeed, there is a close correlation between years of supervised schooling and incidence rates of breast cancer. Few investigators, however, would conclude that the academic environment alone somehow induces cancer.

There are a number of reproductive variables which seem to modify the probability of breast cancer. A heightened risk of breast cancer is associated with women who never married; and amongst the married, women with few or no pregnancies; and, in women with early menarche. On the other hand, premature menopause, either spontaneous or surgically induced, is associated with lower rates of breast cancer. Some sort of relationship between breast cancer and estrogen metabolism also prevails in breast cancer in males. Breast cancer is more common in males with chronic liver impairment or with Klinefelter's syndrome, both of which are associated with higher circulating levels of estrogen.

Ionizing radiation exerts some measurable influence. Hiroshima women 10 to 19 years old who had been exposed to atomic bomb radiation developed significantly higher breast cancer rates than women, similarly exposed, who were older than 35 years, or women who had never been exposed to ionizing radiation.

Are there genetic factors operative in breast cancer? The risk of breast cancer is substantially greater in women whose mother or sister had similar disease. Familial tendencies are particularly frequent in women with bilateral breast cancer. Finally, there are a number of unusual forms of hereditary breast cancer associated with: 1) ovarian cancer; 2) disseminated cancers including gliomas, lung cancer and leukemia, the SBLA syndrome; and 3) Cowden's disease, a rare autosomal disorder with facial trichilemmomata and breast cancer.

Stanley M. Aronson, MD

The Language of Epidemiology (VII). Screening Tests

Preventive medicine may intervene at various stages during the course of a disease. *Primary prevention*, such as immunization against influenza, may prevent disease by neutralizing a risk factor. *Secondary prevention*, such as screening mammography or stool tests for occult blood in asymptomatic individuals, may discover early or latent disease more amenable to treatment. *Tertiary prevention*, such as weight reduction or exercise post-myocardial infarction, may lessen disease progression or recurrence by diminishing contributory risk elements.

Screening is an organized community attempt to detect disorders or risk factors in apparently healthy persons. Screening tests are not intended to be precisely diagnostic. A good screening test separates, with a high likelihood of validity, those individuals who may benefit from further evaluation from those in whom no further evaluation is warranted. The basic features of an effective screening test are : high sensitivity (ie, an abnormal result is found in a high proportion of people actually having the disease), high specificity (ie, a normal result is found in a high proportion of people not having the disease), and high predictive value (accuracy in separating individuals having and not having the screened disorder among those with an abnormal and normal test result, respectively).

Features of a Good Screening Test

In addition to high sensitivity and specificity, a screening test should possess other characteristics. The prevalence of the disorder screened for should be high enough to warrant screening. Its health implications should be serious enough to justify the needed expense and effort. Ideally the test should be simple, inexpensive and acceptable to patients. Furthermore, evidence should exist that effective treatment of disease at an early state will, in some way, be simpler and more effective than at a later, unscreened stage.

From a social policy perspective, screening should be available to those individuals most likely to benefit, should be of a magnitude that does not overwhelm finite health resources, and should allow appropriate compliance.

Selection Bias in Screening

Individuals who have routine health checkups or are volunteers for screening are not proxies for the entire population. Volunteers tend to be healthier, more compliant, and have lower all-cause morbidity and mortality than the general population. Thus, unless studies are well-designed, advantages in outcome in screened individuals may simply reflect pre-existing behaviors or attributes of healthy volunteers.

Lead-time Bias in Screening

Lead-time is the interval between detection of a disease via screening and the time when symptoms would have customarily led to the diagnosis. Screening at times may merely lengthen the time of diagnostic aware-

ness without altering the outcome (eg, screening chest x-ray for carcinoma of the lung). To avoid such lead-time bias or zero-time shift, the screened disease must be one for which early diagnosis results in improved prognosis and the screening test must be sensitive enough to detect early disease.

Length-time Bias in Screening

Screening is more effective with slowly advancing disease. Individuals with a more prolonged course generally have a better prognosis than individuals with more virulent, rapidly progressive disease who tend to come to medical attention unscreened. Screened patients seem therefore to fare better.

Risks in Screening

Screening may be harmful. A diagnosis may be incorrect leading to a false sense of security in patients with false negative tests, and the consequences of needless treatment in those with false positive results. Screening may also lead to overinvestigation of equivocal results and overtreatment of early disease which might never have become manifest (ie, early prostate cancer). Individuals may suffer from a "self-labelling effect" after diagnosis of a disorder such as mild hypercholesterolemia or hypertension. The misperception of illness may be associated with adverse consequences such as increased time lost from employment or the emotional burden of inhabiting "the land of the sick" rather than that of the healthy.

Screening Saves Lives

Prevention or early diagnosis of disease are cornerstones of quality health care. Appropriate screening programs save lives, reduce monetary costs of disease, and mitigate the burden of suffering. Carefully designed studies are needed to evaluate the utility and validity of each screening test and to assess those currently used screening programs in order to avoid biases and unintended consequences.

Edward R. Feller, MD

The Father of All Scientific Journals

Medical periodicals regularly bring us new findings, new interpretations and richer insights into the human struggle against disease and disability. Indeed, the broadcasting of ideas, which alone justifies the existence of our journals, is the indispensable attribute distinguishing sciences from other human endeavors.

We are now awash in medical publications, and their numbers mount each year. Where did this novel, if occasionally burdensome, idea begin? Who was the entrepreneur who brokered the marriage between those who were compelled to share their discoveries with those longing to learn new secrets of nature? Who is answerable for this new literary genre?

The origins of the periodically published scientific archive can be traced to London in the early decades of the seventeenth century. A small cluster of scientists, informally led by Robert Boyle, professed interest in the new experimental philosophy; they met weekly at the Bull-Head Tavern, Cheapside, London for the purpose of ". . . *promoting of Physico-Mathematicall Experimentall learning.*" On November 28, 1660, the group declared itself to be a Society and twelve men assembled to hear Christopher Wren deliver a learned paper. The group flourished and a royal charter was obtained in October of 1661 designating it as the Royal Society of London for Improving Natural Knowledge. Now the oldest scientific society in continuing existence, it is referred to more commonly as the Royal Society.

The Royal Society convened initially in Gresham College but was displaced, following the Great Fire of London, September, 1666 to Arundel House. The responsibilities of the Society inevitably expanded as its combined membership embraced the more creative scientists of Great Britain. The Society was assigned such functions as the standardization of weights and measurements, calendar modifications, the Royal Observatory in Greenwich, geodetic surveys and numerous exploratory sea voyages (including those of Cook). The Society's private library and museum were made public in 1781 forming the nucleus of the British Museum.

Henry Oldenburg was a German transplanted to London. He was born in Bremen in the year 1617, the son of an eminent physician. He had been well educated and in his late youth was assigned the formidable task of negotiating with Oliver Cromwell to protect the mercantile interests of the port of Bremen. While in London Oldenburg became friends with John Milton, Thomas Hobbes, and particularly, with the great physicist Robert Boyle. "*I have begun to enter into companionship with some few men who bend their minds to the more solid studies rather than to others, and are disgusted with Scholastic Theology and Nominalist Philosophy.*" He wrote, "*They are followers of nature itself and of truth.*" When the Royal Society formally began in 1660, Oldenburg was selected as its first Secretary. His responsibilities included the maintenance of the Society's archives. Beyond this, he personally maintained an active correspondence, customarily in Latin, with the scientific communities of the European continent. His numerous letters pleaded that these distant scientists share their latest observations and experiments with the membership of the Society, something most of them were quite willing to do since such letters established dates and affirmed the provenance of their idea or discovery. Oldenburg's incessant correspondence opened up hitherto uncharted channels for the sharing of new, often puzzling and sometimes conflicting, experimental data in mathematics, as well as the physical and biological sciences. Within a short time, his office became the repository for new conjectures and the scientific message center for western Europe.

The immense value of these many letters suggested to Oldenburg that a more enduring and more public form of archive was needed. On March 6, 1664, he assembled the most recent of

these letters into a novel 16 page publication with the oppressive title: *Philosophical Transactions: giving some Accompt of the Present Undertakings, Studies, and Labours, of the Ingenious in Many Considerable Parts of the World.* The publication, which continues to this day, is known more succinctly as *Phil. Trans.*, and is considered the inaugural journal of the worldwide scientific community.

Occasionally, the Royal Society received manuscripts too lengthy to include in the *Phil. Trans.* It then undertook to publish the manuscript in text form, such as its 1686 publication of Isaac Newton's *Philosophiae naturalis principia mathematica.*

In 1832 the abstracts of the many submitted papers formed the basis for a modified publication called the *Proceedings of the Royal Society.* The *Phil. Trans.* in 1887, was then divided into section A (mathematics and physics) and section B (biology and medicine).

As *Rhode Island Medicine* observes its 75th anniversary, intimidated only slightly by the 327th anniversary of *Phil. Trans.*, it is appropriate to recognize anew how all of these publications, large or small, started. Glanvill, a contemporary of Oldenburg, described the published *Philosophical Transactions* as a "*... great ferment of useful and generous knowledge.*" Certainly Oldenburg's great invention has instructed the scientific journals of the world – from the most prestigious to the most parochial – that our mission is uniform, simple and unchanging: The gathering and the sharing of worthy ideas.

Stanley M. Aronson, MD

February 1992

RHODE ISLAND MEDICINE

The Future of Anesthesiology

Guest Editor:

Kathleen Hittner, MD

A critical health problem for your patient. A difficult problem for you to treat.

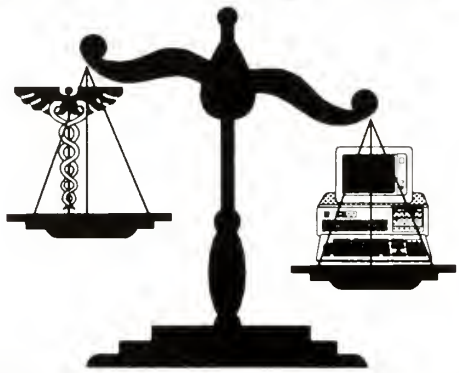
The Miriam Hospital Weight Management Service offers treatment programs addressing all levels of obesity. With over 10 years' experience in obesity treatment and research, our multidisciplinary team provides the resources needed for safe, medically monitored weight loss and for long-term success in maintaining weight loss.

For more information on our programs, or to refer a patient, call:
(401) 861-0870

Portions of our programs may be covered by health insurance.

The Miriam Hospital Weight Management Service
Division of Behavioral Medicine
An affiliate of the Brown University Medical School

BALANCE THE MEDICAL SIDE OF YOUR PRACTICE WITH THE BUSINESS SIDE



Vanguard Medical Management Services gives you and your staff more time for the medical side of your practice.

You love medicine. You and your staff are devoted to providing the best patient care possible. But, the business side of your medical practice is becoming more and more demanding. Frequent and complicated changes in medical insurance claims processing and accounting procedures are pulling your office staff away from medical and patient care services over to the business side of your practice. Maybe it's time to add a medical management service to your practice.

Vanguard Medical Management Services offers a comprehensive practice management service designed to free you and your office staff from time-consuming accounting and claims processing chores, plus provides qualified office staff for short, long-term and permanent assignments. Our team of experienced professionals help you and your staff manage the business side of your practice more efficiently, giving you more time to devote to your patients. You can trust us to provide:

- ✔ *Guarenteed revenue maximation*
- ✔ *Fast, accurate electronic claims processing for commercial insurance carriers, Blue Shield, HMOs, Medicare and Medicaid.*
- ✔ *A knowledgeable service representative dedicated to your practice*
- ✔ *Professional accounting/payroll services*
- ✔ *A confidential evaluation of your fee schedules*
- ✔ *Permanent and temporary staffing services*
- ✔ *Courteous, understanding and helpful response to your patients' billling questions.*

Call Geri Matraia at **(508) 842-4947** or **1(800) 743-2888** for information about putting **Vanguard Medical Management Services** to work for your practice.
New client consultations are free.

512 West Main Street, Shrewsbury, MA 01545

Evaluating a Mass Media Campaign to Promote Screening Mammography in Rhode Island

John P. Fulton, PhD
Judith P. Feldman, MD, MPH
Edward F. Donnelly, RN, MPH
Jay S. Buechner, PhD
Dolores DiOrio, MEd
Barbara A. DeBuono, MD, MPH
Robert A. Smith, PhD
H. Denman Scott, MD, MPH

Many women are still unaware of screening mammography. Some have misunderstandings about it, or attitudes unsupportive of screening.

Screening mammography can prevent a substantial proportion of breast cancer deaths,[1-7] but is greatly underutilized.[8,9] Multiple barriers stand between current reality and screening goals. Screening mammography may be costly, especially for those without adequate health insurance.[10-17] It may be geographically or temporally inaccessible.[12,13,18,19] Physicians may be ambivalent about promoting its use.[20] Many women are still unaware of screening mammography.[9] Some have misunderstandings about it, or attitudes unsupportive of screening.[11,18,21-27] The complexity of the problem calls for multiple, coordinated solutions.

One solution of proven effectiveness is the promotion of screening through mass media channels.[28-36] Although media campaigns are rather ineffective against system barriers, they can reduce individual barriers by increasing awareness, changing attitudes, and reinforcing behavior.[35-37] Campaigns may be directed at small homogeneous populations by fitting media channels and messages to the social and cultural characteristics of recipients,[37] or at large heterogeneous populations by enlisting multiple channels and a variety of congruent messages.[31,38-40] Although promoting a screening test is complex, the principles of success are simple. The promotion must reach a high proportion of people likely to benefit from screening.[41] Promotional messages should describe the screening procedure and its recommended frequency, explain its need, assure its effectiveness and safety, and suggest safe and appropriate sources of screening.[37,39] Upbeat messages are more likely to promote screening than ones that engender fear.[37]

John P. Fulton, PhD, is the Administrator of the Rhode Island Cancer Registry at the Rhode Island Department of Health and a Clinical Assistant Professor of Community Health at Brown University, Providence, Rhode Island.

Judith P. Feldman, MD, MPH, is the Acting Medical Director of Disease Control at the Rhode Island Department of Health and a Clinical Assistant Professor of Medicine at Brown University, Providence, Rhode Island.

Edward F. Donnelly, RN, MPH, is an Epidemiologist in the Office of Chronic Disease at the Rhode Island Department of Health, Providence, Rhode Island.

Jay S. Buechner, PhD, is Chief, Office of Health Statistics at the Rhode Island Department of Health and a Clinical Assistant Professor of Community Health at Brown University, Providence, Rhode Island.

Dolores DiOrio, MEd, is Chief, Office of Epidemiology and Communicable Diseases at the Rhode Island Department of Health, Providence, Rhode Island.

Barbara A. DeBuono, MD, MPH, is Director of Health for the State of Rhode Island and a Clinical Assistant Professor of Medicine, Brown University, Providence, Rhode Island.

Robert A. Smith, PhD, is an Epidemiologist in the Division of Chronic Disease Control and Community Intervention, Center for Chronic Disease Prevention and Health Promotion, Centers for Disease Control in Atlanta, Georgia.

H. Denman Scott, MD, MPH, is Associate Executive Vice President for Health and Public Policy, American College of Physicians, Philadelphia, Pennsylvania.

ABBREVIATIONS USED:

ACS: American Cancer Society

As an integral part of its statewide breast cancer screening program (the program), the Rhode Island Department of Health promoted screening mammography between November, 1987 and December, 1988, focusing on women who had never received a screening mammogram. The media campaign stressed the need for breast cancer screening and the safety of mammography, relying heavily on newspaper advertisements and direct mail to young eligible women. Television and radio news spots were exploited as opportunities arose, and billboards were utilized for one month. Physicians were sent two direct mailings to enlist their cooperation in the program.

To evaluate the campaign's effects, statewide samples of Rhode Island women ages 40 and over were interviewed before and after the 14 months of intensive promotion. The media campaign achieved substantial market penetration in 15 months, and may have affected women's perceptions about breast cancer and mammography, although new screening users were substantially exposed to national as well as local screening publicity in this period. Between the two surveys, 15% of Rhode Island women ages 40 and over received mammograms for the first time. New screening users were distinguishable from unscreened women on the basis of sociodemographics, perceptions and knowledge relevant to screening mammography, and providers' recommendations. Many women who remained unscreened at the time of the follow-up survey have little education, low family income, and less than average contact with medical care.

Methods

As described in previous reports,[42-43] two independent, statewide samples of Rhode Island women age 40 and over were interviewed about knowledge, attitudes, and practices related to breast cancer screening. The first sample (N=852) was interviewed in September and October of 1987, immediately before Rhode Island's statewide breast cancer screening program opened (baseline survey; baseline sample). The second sample (N=856) was interviewed in January, February, and March of 1989, after the program had operated for 14 months (follow-up survey; follow-up sample). In both surveys, respondents were located with random digit dialing. The interviews contained questions on sociodemographics, perceptions, knowledge, and providers' recommendations. The follow-up survey also contained questions about knowledge of the program.

Promotional messages should describe the screening procedure and its recommended frequency, explain its need, assure its effectiveness and safety, and suggest safe and appropriate sources of screening.

In April, 1989 all women receiving mammograms at 35 of 38 mammography sites in Rhode Island were asked to complete a short marketing survey relating to exposure to local and national publicity about mammography. It is estimated that 75% of women receiving mammography in April, 1989 completed a questionnaire. The responses of 637 first-time users of screening mammography were used to study exposure to particular sources of breast cancer screening publicity (Table 4). In the present report, this sample is distinguished from the two statewide samples (baseline and follow-up samples) by referring to it as the "marketing sample."

Responses to all three surveys were used to construct frequency distributions and cross-tabulations (Tables 1-4, 6). Student's t-test was used to assess the statistical significance of selected differences of proportions.

Responses from the follow-up survey were also used to perform logistic regression analyses with SAS Logist software,[44] (Table 5). Regression coefficients (betas) were converted to odds ratios by computing e to the beta power for each.

Synopsis of the Publicity Campaign

Newspapers: The media campaign was initiated at the beginning of No-

Table 1. **Chronology of Publicity for the Rhode Island Breast Cancer Screening Program: November, 1987-December, 1988**

Fourth Quarter, 1987
–Press conference introduces Breast Cancer Screening Program
–Advertisements in one statewide newspaper and three regional papers
–Talk given to American Cancer Society volunteers
–Guest appearances on 4 television programs and 4 radio programs
First Quarter, 1988
–Advertisements in one statewide newspaper and three regional papers
–Newspaper article on mammography
–Talk given to American Cancer Society volunteers
–Guest appearances on 3 talk-radio programs
–Mailing to all licensed MDs
Second Quarter, 1988
–Advertisements in one statewide newspaper and three regional papers
–Public service announcement distributed to all television stations
–Posters distributed to hospitals, radiologists, hairdressers
–Pilot mail campaign to all eligible state employees
Third Quarter, 1988
–Advertisements in five local newspapers
–11 billboards faced
–Mailing to all licensed, private care MDs
Fourth Quarter, 1988
–Mailing to all women ages 40-55 with RI driver's license
–3 short television spots during breast cancer awareness week
–1 live television newscast
–Guest appearances on 1 cable television program and 1 radio program
–Public service announcement distributed to all radio stations

vember, 1987 with a press conference (Table 1). A newspaper with statewide coverage followed with a lead story and editorial. Advertisements were run every two weeks in a newspaper with statewide coverage and in three newspapers with regional coverage between November, 1987 and June, 1988.

Television and Radio: Immediately following the news conference, program staff began making guest appearances on local television and radio programs. Eight separate appearances were made before the first of the year, followed by additional appearances in the first and last quarters of 1988. Public service announcements first appeared on television in the second quarter of 1988, and on radio in the fourth quarter.

Talks: In collaboration with the American Cancer Society (ACS), program staff gave talks to ACS volunteers who trained women in breast self-examination. The volunteers were asked to promote the use of screening mammography and distribute the program's telephone number for information. Talks were given in the last quarter of 1987 and the first quarter of 1988.

Posters and Billboards: Posters promoting the use of screening mammography were distributed to all hospitals, radiology facilities and hairdressing salons in the second quarter of 1988. A one-month billboard campaign was run in the third quarter. One billboard was positioned on a heavily traveled interstate highway, and ten were positioned on heavily traveled local highways.

Direct Mailing to Young Eligible Women: In the fourth quarter of 1988 a direct mailing was sent to all women ages 40-55 with current Rhode Island driver's licenses. The mailing contained a brochure promoting the use of screening mammography and a letter from the Governor, sealed in an envelope from the Governor's office.

Direct Mailings to Physicians: In the first quarter of 1988 all Rhode Island physicians were sent a letter describing the program, asking them to promote the use of screening mammography. The letter described the progress which had been made throughout the state in obtaining state-of-the-art mammography equipment and the measures in place to assure the quality of mammography. In the third quarter of 1988 all physicians in private practice were sent statistics on screening mammography in Rhode Island and asked again to promote its use.

Table 2. **Percentage of Women Targeted for Publicity[a] who Reported Awareness of the Breast Cancer Screening Program, by Age, Education, Income, and Medical Care Utilization, Rhode Island 1989 (N=401)**

Sociodemographics	Percentage Aware of Program
All Women	62%
Age	
40-49	66
50-64	58
65 and over	62
Education	
<HS diploma	63
HS diploma	59
>HS diploma	64
Family Income	
<200% of poverty	59
>200% of poverty	63
General Medical Care	
Have regular provider	62
No regular provider	60
Gynecological care	
Have regular source	63
No regular source	55

[a]Including women ages 40 and over who had not received a mammogram before the start of the Breast Cancer Screening Program.
Source: Statewide survey of Rhode Island women ages 40 and over, 1989.

Results

The media campaign achieved substantial market penetration in the 14 months between the baseline and follow-up statewide surveys (Table 2). Six-tenths of the target population (women who had never used mammography at the time of the first survey) had heard of the breast cancer screening program by early 1989. Market penetration was good in most socio-demographic subgroups, even groups with modest education and low family income.

Market penetration was good in most socio-demographic subgroups, even groups with modest education and low family income.

Women in the target population who reported awareness of the program were more likely than others to feel susceptible to breast cancer, and to believe in the safety of screening mammography (follow-up, statewide samples Table 3). Knowledge of screening recommendations was about equal in the two groups.

First-time mammography users who were surveyed 17 months after the start of the program were more likely to have remembered screening publicity from a national source than a local source (marketing sample; Table 4). Exposure to magazine articles and television specials were reported by more than one-third of first-time users. Among local publicity sources, newspapers were reported most frequently. Friends and relatives were mentioned as a source of information by 38% of respondents.

Logistic regression analysis was performed to test the effectiveness of perceptions and knowledge as predic-

tors of receiving a first screening mammogram after the start of the breast cancer screening program (follow-up, statewide sample Table 5). Among women who had not had a mammogram at baseline, those who believed in the safety of mammography and those who knew screening recommendations for mammography were three times as likely as other women to have received a first screening mammogram 15 months later. Perceived susceptibility to breast cancer and perceived effectiveness of mammography were not predictive of screening. Neither were age, education, and income, which were added to the analysis as control variables.

The profile of women who had never used mammography changed between baseline and follow-up statewide surveys (Table 6). They became younger, were less likely to feel susceptible to breast cancer, and more likely to believe screening mammography safe. Among women who had never used mammography at the time of the second survey – the target group of future programmatic efforts – substantial proportions were of low educational attainment, lived on low family incomes, and did not have regular providers of primary medical care.

Table 3. **Percentage of Women Targeted for Publicity[a] who Reported Specific Perceptions of Breast Cancer and Mammography and who Demonstrated Knowledge of Age-Appropriate Screening Guidelines, by Awareness of the Breast Cancer Screening Program, Rhode Island 1989 (N=401)**

	Percentage Reporting Perception or Demonstrating Knowledge	
Perceptions and Knowledge	Not Aware of Program (N=155)	Aware of Program (N=246)
PERCEPTIONS		
Felt susceptible to breast cancer	25	32
Believed screening mammography effective	46	47
Believed screening mammography safe	62	72
KNOWLEDGE		
Knew screening recommendations	52	50

[a]Including women ages 40 and over who had not received a mammogram before the start of the Breast Cancer Screening Program.

Source: statewide survey of Rhode Island women ages 40 and over, 1989.

Table 4. **Percentage of Women Receiving Screening Mammograms for the First Time who Reported Exposure to Particular Sources of Breast Cancer Screening Publicity, Rhode Island, April 1989 (N=637)**

Geographical Coverage/Medium	**Percentage Reporting Exposure**
PREDOMINANTLY LOCAL	
Newspapers	21
Lectures	15
Direct Mail	12
Billboards	5
PREDOMINANTLY NATIONAL	
Magazine articles	41
Television special	36
Television advertisement	25
OTHER	
Friends and relatives	38

Source: survey of women using mammography in Rhode Island, April 1989.

Discussion

The media campaign appears to have reached its primary target group: Rhode Island women ages 40 and over who had never received a screening mammogram. Almost two-thirds knew of the program 14 months after its inception. Both the breadth and duration of the media campaign may have contributed to this outcome, although the relative contribution of each cannot be ascertained with available data.

Despite the campaign's heavy reliance on print media, women of low educational attainment and low family income reported knowledge of the program about as frequently as others. However, the duration of the media campaign may have helped in this regard, as word of the program spread from person to person. First-time users listed friends and relatives as a source of information only slightly less frequently than magazine articles, the most frequently listed source.

Feelings of susceptibility to breast cancer and the perception that mammography is safe appear to have been related to awareness of the program. Both points were stressed in the media campaign. Screening recommendations were also widely publicized, but no relationship was found between awareness of the program and knowledge of recommendations. It is possible that screening frequency was of less relevance to the target population – women who had never had a mammogram – than reasons for having a mammogram at all. Furthermore, apparent connections between program awareness and attitudes or knowledge may be spurious based on dependent relationships between these variables and exposure to national publicity. First-time users of mammography were more likely to report national than local screening publicity, demonstrating the strong presence of national publicity in Rhode Island. Women whose attitudes about screening had been altered by national publicity may have been more ready to hear the messages of local publicity.

Perceptions and knowledge were

Table 5. **Results of Logistic Regression Analysis[a]: Perceptions and Knowledge as Predictors of Receiving a First Screening Mammogram after the Start of the Breast Cancer Screening Program, Controlling for Age, Education, and Income, Rhode Island 1989 (N=401)**

Predictors	Odds Ratio	95% Confidence Interval
PERCEPTIONS		
Felt susceptible to breast cancer	0.79	(0.47-1.31)
Believed screening mammography effective	0.66	(0.40-1.10)
Believed screening mammography safe	3.10	(1.59-6.03)
KNOWLEDGE		
Knew screening recommendations	2.94	(1.67-5.20)
SOCIODEMOGRAPHICS		
Ages 40-49	0.88	(0.50-1.55)
Ages 65 and over	0.90	(0.46-1.74)
Education <HS diploma	0.58	(0.32-1.07)
Education >HS diuploma	0.83	(0.45-1.52)
Income >200% of poverty	1.35	(0.78-2.34)

[a] R=0.27

Source: statewide survey of Rhode Island women ages 40 and over, 1989.

Table 6. **Characteristics of Women age 40 and Over who had Never Used Mammography, Rhode Island 1987 and 1989**

Characteristics	Percentage 1987 (N=379)	1989 (N=289)
SOCIODEMOGRAPHICS		
Age 40-64	58	66
Schooling <HS diploma	38	37
Family income <200% of poverty	52	53
MEDICAL CARE UTILIZATION		
Have regular general medical provider	77	75
Have regular souce of gynecological care	80	76
PERCEPTIONS		
Felt susceptible to breast cancer	36	26
Believed screening mammography effective	40	46
Believed screening mammography safe	47	61
KNOWLEDGE		
Knew screening recommendations	38	41

Source: statewide surveys of Rhode Island women ages 40 and over, 1987 and 1989.

useful in distinguishing new users of mammography from never users, after controlling for age, education, and income. Among perceptions about breast cancer and mammography, believing that screening mammography is safe had a discernible effect on screening status. Feeling susceptible to breast cancer and believing that screening mammography is an effective screening tool did not. In previous studies, screening behavior has usually been related more strongly to perceptions of safety and effectiveness than feelings of susceptibility.[27,45-48] Knowledge has also been found to predict screening.[14,27] In Rhode Island, local publicity may have enhanced feelings of susceptibility to breast cancer, but apparently to no avail. Local publicity may also have increased the perception that mammography is safe, in which case it may have contributed to the increase in ever-screened women. The Rhode Island experience illustrates the potential importance of positive messages[37] and the potential futility of negative messages in screening promotions. To the extent that knowledge of screening guidelines had a similar effect, other antecedents must be considered, such as national publicity or the work of health care professionals in the state. In any case, the design of Rhode Island's statewide publicity program, confounded by the effects of national publicity and lacking a control population, frustrates attempts at direct attribution.

The Rhode Island experience illustrates the potential importance of positive messages and the potential futility of negative messages in screening promotions.

After 14 months of the program, the target population had grown smaller and younger. Also, its perceptions of breast cancer and mammography had changed. Although never-screened women were less likely to feel susceptible to breast cancer, they were more likely to believe screening mammography safe. This augurs well for the future, given the apparent importance of these perceptions for screening behavior.[27,45-48] The latter (perceiving mammography as safe) appears to be an antecedent of screening, while the former (feeling susceptible to breast cancer) may not be. In short, the population of never-screened women may have been attitudinally readier for screening in 1989 than 1987, possibly as a result of local publicity.

During the first 14 months of the program, the media campaign used many channels, targeting a large, heterogeneous population of eligible women who had never used mammography. In that time, the size of the target group diminished, but its heterogeneity remained largely intact. This suggests the continuation of a broad-based media campaign to promote screening mammography in Rhode Island. New efforts should deemphasize susceptibility to breast cancer, a negative message that had no apparent effect on screening behavior. Also, new efforts should re-empha-

size the effectiveness of screening mammography, based on previous research.[27,45-48]

The sampling design of the Rhode Island surveys precludes analysis of the campaign's effectiveness among socioeconomically disadvantaged racial and ethnic minority groups. Even though the campaign appears to have reached women of modest educational attainment and low income, disadvantaged minority women (who represent a minority of all disadvantaged women in Rhode Island) may not have been reached as effectively. In fact, breast cancer mortality rates in Rhode Island indicate a disproportionate need for screening mammography among black women, many of low income.[49] In response, the Rhode Island Department of Health has designed a special breast cancer screening program which focuses on black women of low income, including a media campaign with specially selected channels; radio stations targeting adult blacks, a black-owned newspaper, posters for distribution in black neighborhoods, and brochures to be distributed by black women and members of black sororities.

. . . breast cancer mortality rates in Rhode Island indicate a disproportionate need for screening mammography among black women.

In the future, evaluation feedback will become more critical to the efficiency of media campaigns for the promotion of screening mammography in Rhode Island and elsewhere. As the target population diminishes in size, distinctive sub-populations of harder-to-reach women will emerge, necessitating a switch from broad-based media coverage to specialized, targeted media campaigns. This process is best guided by regular surveillance, to describe the target sub-populations as they change, to guide the selection of media channels, and to choose the foci of media messages. Surveillance is also useful in guiding the reallocation of resources between efforts to promote screening and efforts to make screening more accessible, by determining the relative utility of each for different sub-populations, and finally, in guiding the phase-out of regular mass media campaigns in favor of less costly promotional efforts.

This study was supported in part by Cooperative Agreement No. U50/CCU102929-01-1 from the Division of Chronic Disease Control and Community Intervention, Center for Chronic Disease Prevention and Health Promotion, Centers for Disease Control.

References

1. Shapiro S, et al.: Ten to fourteen-year effect of screening on breast cancer mortality. JNCI 69:349-355 (1982).
2. Tabar L, et al.: Reduction in mortality from breast cancer after mass screening with mammography. Randomized trial from the Breast Cancer Screening Working Group; the Swedish National Board of Health and Welfare. Lancet 1(8433):829-932 (1985).
3. Baker LH. Breast Cancer Detection Demonstration Project: Five-year summary report. CA, A Cancer Journal for Clinicians 32:194-225 (1982).
4. Baker LH, Chin TDY, Wagner KV. Progress in screening for early breast cancer. J Surg Oncol 30:96-102 (1985).
5. Verbeek A. et al. Reduction of breast cancer mortality through mass screening with modern mammography. First results of the Nijmegen project, 1975-1981. Lancet 1(8388):1222-1224 (1984).
6. Colletee HJA, Day NE, Robmach JJ, and DeWaard F. Evaluation of screening for breast cancer in a non-randomized study (the DOM project) by means of a case-control study. Lancet 1(8388):1224-1226 (1984).
7. Council on Scientific Affairs: Mammographic Screening in asymptomatic women aged 40 years and older. JAMA 261:2535-2542 (1989).
8. Dawson DA. Breast cancer risk factors and screening: United Sates, 1987. National Cancer Institute for Health Statistics. Vital Health Stat 10(172) (1989).
9. Heath CW, et al. Trends in screening mammograms for women 50 years of age and older – Behavioral Risk Factor Surveillance System, 1987. MMWR 38 (9):137-140 (1989).
10. Anda RF, Sienko, DG, Remington PL, Gentry EM, Marks JS: Screening mammography for women 50 years of age and older: practices and trends, 1987. Am J Prev Med 6(3) 123-129 (1990).
11. Bassett LW, Fox SA, Pennington E, Gold RH: Mammographic screening in southern California 2-1/2 year longitudinal study. Radiology 173:61-63 (1989).
12. Bloom DL. Physicians' knowledge, attitudes and behavior concerning mammography. An in-depth telephone interview study. Office of Cancer Communications, National Cancer Institute, Bethesda, Maryland, June 1990.
13. Burack RC, Liang J. The early detection of cancer in the primary-care setting: factors associated with the acceptance and completion of recommended procedures. Prev Med 16:739-751 (1987).
14. Burack RC, Liang J. Acceptance and completion of mammography by older black women. Am J Public Health 79:721-726 (1989).
15. Kruse J, Phillips DM. Factors influencing women's decision to undergo mammography. Ob Gyn 70:744-748.
16. Lantz PM, Remington PL, Soref M. Self-reported barriers to mammography: implications for physicians. Wisconsin Med J 602-606 (1990).
17. National Cancer Institute. Mammography screening: state level activities and a review of the literature, National Cancer Institute, Bethesda, MD. March 1989.
18. Rimer BK, Kasper Kentiz M, Kessler HB, et al. Why women resist screening mammography: patient related barriers. Radiology 172:243-264 (1989).
19. Simard A, Paquette L. Baillargeon J, Flaradeau M. Perception of cancer detection and early treatment in a population participating in the national breast screening study in Canada. Canadian J Pub Hlth, 80, 226-227 (1989).
20. American Cancer Society. Survey of physicians' attitudes and practices in early cancer detection. CA, A Cancer Journal for Clinicians 40(2): 77-99 (1989).
21. Fox SA, Klos DS, Tsou CV, Baam JK. Breast cancer screening: the underuse of mammography. Radiology 156:607-611 (1985).
22. French K, et al. Attendance at a breast screening clinic: a problem of administration or attitudes. Br Med J 285:617-620 (1982).
23. Howard J. Using mammography for cancer control: an unrealized potential. CA 37:33-48 (1987).
24. Leather DS, and Roberts MM. Older women's attitudes towards breast disease, self-examination, and screening facilities: implications for communication. Br Med J 290:668-670 (1985).
25. Maclean U, Sinfield D, Klein S, and Harnden B. Women who decline breast screening. J Epidemiol Community Health 38:278-283 (1984).

[26] National Cancer Institute. Women's Attitudes, Knowledge, and Beliefs about Mammography. A focus group interview study. Prospect Associates, Ltd., Rockville, Maryland, 1989.
[27] Rutledge DN, Hartmann WH, Oney-Kinman P, Winfield AC. Exploration of factors affecting mammography behaviors. Prev Med 17:412-422 (1988).
[28] Centers for Disease Control. Trends in screening mammograms for women 50 years of age and older–Behavioral Risk Factor Surveillance System, 1987. MMWR 38:137-140 (1988).
[29] Cole RE, Wagner DE. The pros and cons of a mass-media colorectal screening program. Prog Clin Biol Res 339:325-330 (1990).
[30] Hill D. Rassaby J, Gray N. Health education about breast cancer using television and doctor involvement. Prev Med 11:43-55 (1982).
[31] Kaufman AJ, Worrell J, Bain RS Jr, et al. American Cancer Society's breast cancer detection awareness program: the 1988 middle Tennessee experience. Southern Medical J 83(6):618-620 (1990).
[32] Lane DS, Polednak AP, Burg MA. The impact of media coverage of Nancy Reagan's experience on breast cancer screening. Am J Public Health 79:1551-52 (1989).
[33] Olsen TG, Feeser TA, Conte ET, Schroeter AL. Skin cancer screening–a local experience. J M Acad Dematol 16(3):637-641.
[34] Pennsylvania DOH. Cervical cancer education and detection project. Pennsylvania Cancer Plan, Oct. (1989).
[35] Roberts MM, Robinson SE, French K, et al. Edinburgh breast education campaign on breast cancer and breast self-examination: was it worthwhile? J Epidemiol Comm Health 51:338-343 (1986).
[36] Winchester DP, Lasky HJ, Sylvester J, Maher ML. A television-promoted mammography screening pilot project in the Chicago metropolitan area. CA 38:291-309 (1988).
[37] National Cancer Institute. Promoting Mammography Screening, Ideas & Resources for Public Health departments. No. 90-497. National Cancer Institute, Bethesda, Maryland, 1990.
[38] Norquist JO. Breast Cancer Awareness Task Force, Milwaukee, Wisconsin. City of Milwaukee, Wisconsin, 1989.
[39] Schecter C, Vanchieri CF, Crofton C. Evaluating women's attitudes and perceptions in developing mammography promotion messages. Pub Hlth Rpts, 105(3), 253-257 (1990).
[40] Sobel J, Gordon D, Kristal A, et al. The Oregon Breast Cancer Detection Awareness Project: follow-up of a community-based breast cancer screening campaign. Prog Clin Biol Med 293:75-87 (1989).
[41] Cadman D, Chambers L, Feldman W, Sackett D. Assessing the effectiveness of community screening programs. JAMA 251:1580-1585 (1984).
[42] Buechner JS, Fulton JP, Kaufmann RB, et al. Use of mammography for breast cancer screening – Rhode Island, 1987. MMWR 37:357-360 (1988).
[43] Buechner JS, Fulton JP, Feldman JP, et al. Trends in breast cancer screening – Rhode Island, 1987-1989. MMWR 38:569-571 (1989).
[44] Harrell FE. The LOGIST procedure. In: SAS Institute, Inc., SUGI Supplemental Library User's Guide, 1983 Edition. SAS Institute, Inc, Cary, North Carolina, 1983, pp. 181-202.
[45] Aho, WR. Participation of senior citizens in the Swine Flu Innoculation Program: an analysis of Health Belief Model variables in preventive health behavior. J Gerontol 34:201-208 (1979).
[46] Bodenheimer HC, Fulton JP, Kramer PD: Acceptance of hepatitis B vaccine among hospital workers. Am J Public Health 76:252-255 (1986).
[47] Hallal JC The relationship of health beliefs, health locus of control, and self-concept to the practice of breast self-examination in adult women. Nurs Res 31:137-142 (1982).
[48] Hirshfield-Bartek J. Health beliefs and their influence on breast self-examination practices in women with breast cancer. Oncol Nurs Forum 9:77-81 (1982).
[49] Fulton JP, Buechner JS, Waters WJ. Black/white cancer mortality differentials in Rhode Island: inferences for prevention and screening efforts. RI Med J 72:311-315 (1989).

RHODE ISLAND COMPUTERIZED IMAGING, INC.

Cat Scan Facility
401•751•1110

weekdays
7 am - 5 pm

- Evening appointments for contrast studies
- Medicare, Ocean State
  Rhode Island Blue Cross/Blue Shield approved
- Board Certified Radiologist

Located in: Atwood Medical Center
Suite LL3
1524 Atwood Avenue
Johnston, RI 02919

Work-up of the Abnormal Mammogram for Palpable and Nonpalpable Breast Masses

Barbara Schepps, MD, FACR
Patricia K. Spencer, MD
Francis H. Scola, MD, FACR
William Thompson, MD, FACS

Mammography can reveal breast cancer up to four years prior to clinical detection.

More breast cancer is diagnosed among women in the US than any other cancer. In fact, breast cancer accounts for about a third of all cancers in women, and about one-ninth of all women will develop breast cancer at some time. An estimated 175,000 new cases will be found this year in the US. Breast cancer will claim an estimated 44,500 lives before year's end, 18% of all cancer deaths in women, second only to lung cancer.[1] In Rhode Island alone, it is estimated that 1,000 new cases of breast cancer will be diagnosed and 250 will die of the disease.[1] Among the 50 states, Rhode Island ranked second for its age-adjusted breast cancer mortality in 1986.[2]

Mammography can reveal breast cancer up to four years prior to clinical detection. The primary goal of screening mammography is to detect clinically occult breast cancer and to initiate therapy at a time in the natural history of the disease when mortality reduction can be effected. More than 50 million American women ages 40 and over can benefit from mammographic screening. Various studies have shown that early detection reduces mortality.[3]

In 1963 the Health Insurance Plan of Greater New York undertook the classic blinded study which ultimately demonstrated improved survival with breast cancer screening. The study also demonstrated the superiority of mammography and physical examination together, over physical examination alone.[4] With this information, in 1973, the National Cancer Institute and the American Cancer Society began the Breast Cancer Detection Demonstration Project (BCDDP). The goal of this project was to educate both physicians and the public about the importance of early breast cancer detection. This project was significant since it demonstrated that 41.6% of the cancers detected were found by mammography alone and one third of the cancers were less than one centimeter in size. One third of the cancers were demonstrated in women under age 50.[5,6] Screening projects in both Sweden and the Netherlands also demonstrated significant reduction in mortality in screened populations.[3,7]

To date, breast cancer cannot be prevented. Finding the disease early not only affords the best chance for cure but also allows some latitude in therapeutic modalities. Eleven national societies, including the American College of Radiology, the American College of Surgeons, the American Cancer Society, and the National Cancer Institute have publicized consensus recommendations for screening mammography.[8]

ABBREVIATIONS USED:
BCDDP: Breast Cancer Detection Demonstration Project
FNAB: fine needle aspiration biopsy

Barbara Schepps, MD, FACR, is Director of Mammography, Rhode Island Hospital, Radiologist in the Department of Diagnostic Imaging, Rhode Island Hospital, Radiologist, Women and Infants Hospital, and Clinical Associate Professor of Radiology, Brown University, Providence, Rhode Island.

Patricia K. Spencer, MD, is Radiologist in the Department of Diagnostic Imaging, Rhode Island Hospital, Radiologist, Women and Infants Hospital, and Clinical Assistant Professor of Radiology, Brown University, Providence, Rhode Island.

Francis H. Scola, MD, FACR, is Director of Ultrasound, Rhode Island Hospital, Radiologist in the Department of Diagnostic Imaging, Rhode Island Hospital, Radiologist, Women and Infants Hospital, and Clinical Associate Professor of Radiology, Brown University, Providence, Rhode Island.

William Thompson, MD, FACS, is Acting Chief of Surgery, Rhode Island Hospital and Clinical Professor of Surgery, Brown University, Providence, Rhode Island.

Other imaging modalities have been employed in detecting breast cancer, but to date the mammogram remains the single best tool. Sonography, computed tomography, and magnetic resonance imaging all may play ancillary roles, but none has a proven efficacy in screening.

The Screening Mammogram

The objective of the screening mammogram is to identify clinically occult breast cancer in asymptomatic women at a time when intervention will reduce mortality from the disease and allow for therapeutic options such as breast conservation. To maximize earlier detection of breast cancer and also keep costs low, screening mammography should be separated from diagnostic mammography in the evaluation of patients with breast symptoms and screening mammographic abnormalities. In a properly organized screening setting, a two view study of the highest quality should require less than 15 minutes to obtain. Interpreting batched images at a later time allows for increased efficiency. Double reading increases the sensitivity of interpretations with only minimal cost increase.

Clinical examination of the breast is an important and necessary part of screening for breast cancer, and should be performed in conjunction with the screening mammogram. It is preferable for the clinical exam to be done with or before mammography, but soon afterward is considered acceptable.

Continued compliance with screening guidelines is related to the attitudes of patients and providers, alike. The substance of the mammographic report and its interpretation are important in gaining the support of both groups. Screening mammography should be negative in 85 to 90% of patients at first screening. The number of patients negative at subsequent screenings should be greater than 95%. Five to seven cancers per 1,000 women should be found at first screening. This rate will decrease to the incident level in the population from 0.8 to 3.5 cancers per 1,000 women, on subsequent screens. Patients with positive screening results will require additional work-up to exclude suspicious or questionable lesions.

Other imaging modalities have been employed in detecting breast cancer, but to date the mammogram remains the single best tool.

Mammographic reporting should be concise and employ terminology which conveys the findings as directly as possible. All reports should conclude with a summary of the final assessment. There are no absolute detection guidelines, but many experts suggest that reports use a range of categories between no evidence of malignancy and unequivocal malignancy. An informal classification used internationally provides five such categories.

1. The study is negative. There is nothing further on which to comment.
2. The study demonstrates a benign finding which the radiologist feels should be noted, eg, oil cyst.
3. There is a finding, likely benign, which warrants either additional imaging studies or interval follow-up, less than the usual time between screens, eg, six months.
4. There is an abnormality which is not definitely breast cancer, but is of sufficient concern to consider biopsy.
5. There is a lesion which is most likely breast cancer.

Each mammography report should comment on the mammographic appearance of the parenchyma: normal, fatty, or dense. In studies where findings are noted, the quadrant in which the abnormality is seen should be stated. Some radiologists prefer to ascribe abnormalities to a clock face, but this may confuse both radiologist and clinician.

The size of a mass should be noted, and its appearance described: smooth, irregular, or lobulated in contour. Macrocalcifications should be noted, but microcalcifications require more specific descriptions: clustered or scattered, pleomorphic, of different density, or following a ductal pattern. Skin changes, asymmetric densities, and architectural distortion should be described. Are the findings new or were they present in previous studies? Have they changed appreciably? Do they correspond to a site of previous surgery?

It is important to emphasize that screening for breast cancer is incomplete without clinical breast examination. Correlation of mammographic findings with physical examination of the breasts may elucidate the former. Nonetheless, mammography may reveal nonpalpable findings. Even in the BCDDP, for which today's state-of-the-art film-screen combinations and equipment were unavailable, 41.6% of the breast cancers were detected by mammography alone.[5,6]

Interpreting the Screening Mammogram Report

Parenchymal Appearance

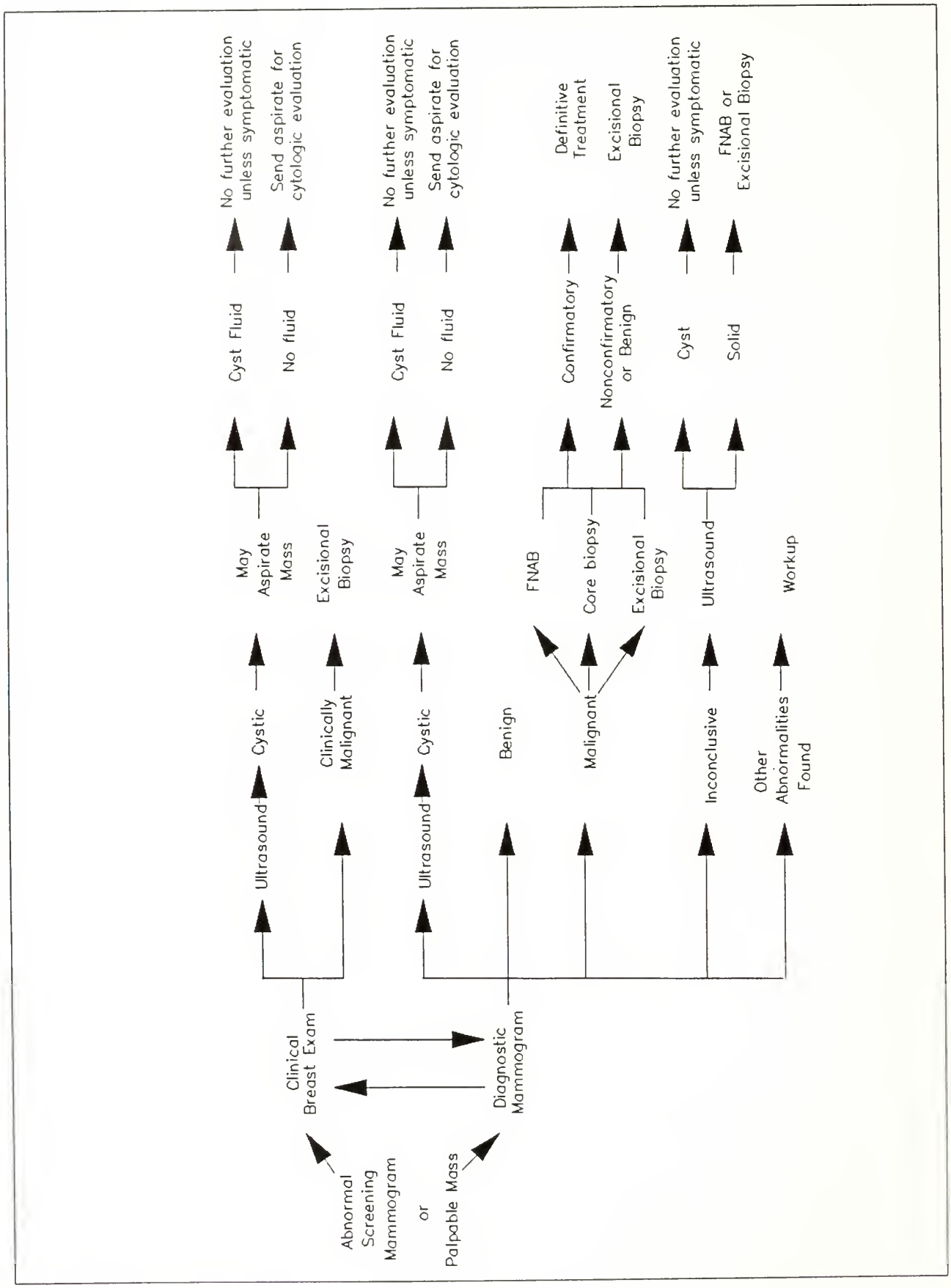
In all mammographic studies there should be comment on the parenchymal appearance. A fatty breast is easy to assess radiographically, and abnormalities are readily detected in most cases. When breast parenchyma is dense, however, interpretation is more difficult. Breast parenchyma is of the same density as soft tissue; dense breast parenchyma may obscure soft tissue masses.

Masses

Reports may also categorize a number of benign entities which warrant comment but should be of no clinical cause for concern. these findings might include microcalcifications scattered diffusely throughout the breast (pathognomonic for adenosis), coarse, popcorn-like calcifications typical for degenerating fibroadenoma, low density masses such as oil cyst lipoma or galactocele, mixed density masses such as a lymph node, or doughnut-like calcifications typically noted on the skin. Smooth, round, or void masses of low density, particularly if unchanged from a previous study, are generally considered benign if less than one centimeter in size. Multiplicity and bilaterality generally favor benignancy.

Masses which are one centimeter or larger and of high density, particu-

Figure 1. **Work-up of the Abnormal Screening Mammogram or Palpable Breast Mass**



larly if unifocal or lobulated, may warrant further evaluation. To assess such a mass, one should begin with the cone compression spot view. This focally compresses the area of interest, separates the stroma, and frequently improves elucidation of mass margins. If a mass has lobulated or irregular margins, further histologic, cytologic, or sonographic evaluation may be warranted.

Sonography is used primarily to evaluate smooth-walled masses. State-of-the-art sonographic equipment is important. A high frequency linear array transducer should be employed. Masses which demonstrate smooth walls, good through-transmission, and are anechoic meet the criteria for simple cysts. No further evaluation is necessary. Cyst puncture may be performed for relief of symptoms. Masses with internal echoes or with margin irregularity warrant aspiration and possible pneumocystography. If no fluid is obtained, the aspirate should be sent for cytologic evaluation. Cyst fluid is not routinely evaluated cytologically. Masses smaller than one centimeter in size may not exhibit all of the classic sonograph signs of cysts, and may warrant further evaluation.

A solitary solid mass of greater than one centimeter in size warrants further histologic or cytologic evaluation. If stereotaxic equipment is available, guided fine needle aspiration (FNAB) or core biopsy may be performed. If such equipment is not available and the mass is not palpable, needle localization and surgical excision may be necessary.

An interval follow-up of less than six months has little merit. It has been demonstrated that changes in masses or calcifications in that time interval are seldom seen, and in the rare instances when such changes occur, appreciable alteration in clinical outcome is minimal. The six-month follow-up has less applicability today than in previous years, because one can evaluate breast abnormalities with a variety of modern imaging techniques which provide immediate diagnoses.

Calcifications

With older mammographic equipment, interval follow-up was frequently necessary to look for increases in the numbers of microcalcifications. Today, with the cone compression spot magnification technique, one may better quantify microcalcifications, and, more importantly, may qualify their character. Greater significance is placed on contour, shape, density, and grouping than number alone. For example, microcalcifications which are irregularly dense and pleomorphic and which follow a ductal pattern are typically associated with ductal carcinoma in situ of the comedo variety. Other appearances may typify other cancers. Stereotactic, cytologic, or histologic assessment of such calcifications may indicate the need for surgical intervention.

About 2% of screened women warrant further intervention.[5,9] These fall into the last two reporting categories. A small subset exhibit the classic appearance of a spiculated mass with or without associated microcalcifications.

The increasing use of stereotactically guided FNAB or core biopsy is changing how nonpalpable lesions are evaluated. Lesions can now be identified and samples taken with accuracy. Stereotactic instruments localize lesions with an accuracy of plus or minus one millimeter. If stereotactic biopsy results occur with a mammographic suspicion of neoplasia, then surgery and therapy may be preplanned. Cytologic diagnosis can be obtained with a sensitivity of 94-97% and a specificity of 93-95%.[10] Core biopsy shows comparable accuracy. In 10-25% of cases, a cytologic diagnosis cannot be made. If this occurs, or if the specimen and mammography results are not in concert, then excisional biopsy is indicated. Excisional biopsy with needle localization of nonpalpable lesions is highly effective and can usually be performed as an outpatient procedure.[11]

The Diagnostic Mammogram

Diagnostic mammography is recommended for patients with breast symptoms such as masses, pain or discharge. It should be performed in all patients prior to cosmetic breast surgery. Diagnostic mammography is done in preoperative patients with breast masses to assess for abnormalities in the ipsilateral or contralateral breast. It is also used to search for primary tumors in patients with metastatic disease, and in women with large breasts which render physical examination difficult.

Diagnostic mammography is negative in approximately 10% of breast cancers. Therefore, a palpable mass which is clinically suspicious for carcinoma should be biopsied, even with a negative diagnostic mammogram.

The Palpable Breast Mass

Patients presenting with a palpable breast mass should be evaluated initially with a physical breast examination and mammography. If the clinician who evaluates the patient initially does not treat breast disease routinely, the patient should be referred to a specialist.

Many breast surgeons will attempt aspiration of all palpable breast masses. If no cystic fluid is aspirated, cytological evaluation is performed.

The diagnostic mammogram study not only evaluates the mass, but also the remainder of the breast and the contralateral breast as well. The palpable mass may well be a cyst, but an occult malignancy may be present elsewhere. Such a finding may alter the patients' therapy. If the palpable lesion is mammographically benign and no other significant abnormalities are demonstrated, the workup can proceed on the basis of clinical findings.

If a palpable lesion proves to be of high density mammographically and cystic sonographically, cyst puncture need not be performed except to alleviate symptoms. If the lesion is equivocal sonographically, cyst puncture and pneumocystography are helpful in further evaluation. A mass which is solid, well circumscribed, and smoothly marginated sonographically is most likely a fibroadenoma. FNAB or excisional biopsy may be useful in these patients. Masses which are stellate or irregular

mammographically should go directly to FNAB or core biopsy. If these results are nonconfirmatory or benign, then excision is recommended. If malignancy is confirmed, then definitive therapy can be initiated.

Women themselves play a pivotal role in the fight to increase survival from breast cancer, a disease whose age-adjusted mortality has shown no improvement in the past 40 years.

Patients who present with bloody nipple discharge may be evaluated with galactography. Galactography can identify an intraductal mass or masses and demonstrate the extent of such lesions. This may be a useful preoperative adjunct. Excision of such a duct is advised.

The ability to alter the natural history of breast cancer is directly related to the quality of screening mammography and the frequency with which it is performed. Women themselves play a pivotal role in the fight to increase survival from breast cancer, a disease whose age-adjusted mortality has shown no improvement in the past 40 years.[12,13]

References

1. Boring CC, Squire TS, Tong T. Cancer statistics, 1991. CA–A Cancer Journal for Physicians 41(1): 19-36 (1991).
2. Centers for Disease Control. Deaths from breast cancer among women–United States, 1986. MMWR 38(33) (1989).
3. Tabar L, Fagerberg G, Duffy SW, Day NE. The Swedish two county trial of mammographic screening for breast cancer: recent results and calculation of benefit. J Epi Comm Hlth 43:107-114 (1989).
4. Shapiro S, Venet W, Strax P, Venet L. Periodic screening for breast cancer: the Health Insurance Plan Project and its sequelae, 1963-1986. Johns Hopkins Press, Baltimore, MD (1988).
5. Baker LH. Breast Cancer Detection Demonstration Project: five year summary report. CA–A Cancer Journal for Physicians 32:194-225 (1982).
6. Seidman H, Gelb SK, Silverberg E. LaVerda N, Lubera JA. Survival experience in the Breast Cancer Detection Demonstration Project. CA–A Cancer Journal of Physicians 37:258-290 (1987).
7. Vebeek ALM, Hendricks JHCL, Holland R, Mravunac M, Suurmans F, Day NE. Reduction of breast cancer mortality through mass screening with modern mammography: first results of the Nijmegen Project, 1974-1981. Lancet 1:1222-1224 (1984).
8. National Medicine Roundtable on Mammography Screening Guidelines. National organizations agree on joint mammography guidelines. News. June, 1989.
9. Tabar L, Gad A. Screening for breast cancer: the Swedish trial. Radiology 138:219-222 (1981).
10. Gent HJ, Sprenger E, Dowlatshahi K. Stereotaxic needle localization and cytological diagnosis of occult breast lesion. Ann Surg 204(5):580-584 (1986).
11. Thompson WR, Bowen R, Dorman BA, Pricolo VE, Shahinian TK, Soderberg CH. Mammographic localization and biopsy of nonpalpable breast lesion. Arch Surg 126:730-734 (1991).
12. US Environmental Protection Agency and National Cancer institute. Cancer Mortality Rates and Trends, 1950-1979. US Government Printing Office, Washington, DC, 1983.
13. Gloeckler Ries LA, Hankey BF, Edwards BK. Cancer Statistics Review 1973-1987. National Cancer Institute, Bethesda, Maryland, 1990.

METRO
JANITORIAL
SERVICES

PROFESSIONAL CLEANING SERVICES

- Offices • Office buildings • Labs
- Bonded and Insured
- Current Clients include:

RIMS MEMBERS
RIDA MEMBERS

421-8661

Breast Cancer Management in the Nineteen Nineties

Francis J. Cummings, MD
Arvin S. Glicksman, MD
Harold J. Wanebo, MD

... the involvement of the patient, herself, in a meaningful decision-making process may be the most important contribution of the last quarter century to the successful management of breast cancer.

The current review will address some common issues in breast cancer management: detection and diagnosis and the need for a multidisciplinary approach using surgery, radiation and chemotherapy. Breast cancer is the most common malignancy among women and accounts for 27% of their cancer and 18% of their deaths from cancer.[1] The risk of women developing cancer in their life time (birth to 100) is stated to exceed 10%. A more meaningful figure is to give the relative cancer risk during defined age periods.[2] Thus, the overall risk of developing breast cancer under age 30 is negligible (.04%), from 35 to 45 it is 0.88%. Between 35 and 55 it is 2.53%, and from 50-110 it is 8.96%. Factors that predictably modify the baseline rate are personal history of breast cancer (opposite breast), a family history of breast cancer in first degree relatives (increases risk by 1.7 to 2.5), and known atypical hyperplasia in the benign or fibrocystic breast as documented by breast biopsy (increases risk by 4.4). Other factors with less predictable effects include early menarche, late menopause, late first pregnancy or no pregnancy, exogenous estrogens, and alcohol. An example of high risk is a woman with atypical hyperplasia and a family history in a first degree relative, who has an 8.9 increased risk.[3]

The treatment of breast cancer in the 1990s is best accomplished by an integrated therapeutic approach which utilizes the technical advances of early detection (diagnostic imaging), the technical skills of the surgical oncologist and radiation oncologist, and the careful application of medical, scientific advances by the medical oncologist. A prospectively applied, integrated medical program provides the patient with opportunities for therapeutic success where the whole is greater than the sum of the individual parts. And the involvement of the patient, herself, in a meaningful decision-making process may be the most important contribution of the last quarter century to the successful management of breast cancer.

Francis J. Cummings, MD, is Attending Physician, Department of Medicine, Roger Williams Medical Center, and Associate Professor of Medicine at Brown University, Providence, Rhode Island.

Arvin S Glicksman, MD, is Chairman, Department of Radiation Oncology, Roger Williams Medical Center, and Professor of Medical Sciences at Brown University, Providence, Rhode Island.

Harold J. Wanebo, MD, is Chief of Surgery, Roger Williams Medical Center and Professor of Surgery and Director of Surgical Oncology, Brown University, Providence, Rhode Island.

ABBREVIATIONS USED:
CALGB: cancer and leukemia group B
CMF: cyclophosphamide, methotrexate, fluorouracil
DCIS: ductal carcinoma in situ
ER: estrogen receptor
FNAC: fine needle aspiration cytology
LCIS: lobular carcinoma in situ
L-PAM: l-phenylalanine mustard
NSABP: National Surgical Adjuvant Breast Project
PLM: percent labelled mitoses
SECSG: Southeast Cancer Study Group
SWOG: Southwest Oncology Group
VP: vincristine, prednisone

Detection and Diagnosis

All women over age 20 should have routine annual breast exams by their physicians and be taught breast self examination. All women by the age of 50 should have regular mammograms at yearly intervals. It appears to be advantageous for mammograms to be taken every 2-3 years while the woman is still in her forties and have a baseline mammogram while in her thirties. Women with high risk factors should undertake a regular mammography program at an earlier age.

Detection and diagnosis are determined by the size of the lesion and whether it is palpable or not and the mammographic findings in the breast. Women who present with palpable lesions are candidates for biopsy by fine needle aspiration cytology (FNAC). A mammogram is required to determine whether there are other nonpalpable lesions in the breast or in the opposite breast. In the patient with a cancerous nodule, the sensitivity ranges between 75-95% in the adequately sampled specimen.[4,5] A negative biopsy usually requires a confirming open biopsy (a false negative rate between 5-10% may occur due to sampling).[6] In the event the FNAC is positive for cancer, the surgeon may discuss with the patient the various options for treatment and plan accordingly.

Patients with non palpable lesions demonstrated by mammography will require open biopsy, usually using needle localization. Non-palpable mammographic lesions prompting biopsy usually include asymmetric densities, microcalcifications in clusters or in branched chains or may occasionally include spiculated irregular density, highly suggestive of cancer. The radiologist places a wire into the proximity of the lesion, which guides the surgeon in performing the biopsy. A specimen mammogram confirms that the lesion is included in the biopsy. A frozen section is done on all palpable lesions and grossly suspicious needle localized lesions to ensure adequate specimen for hormone receptors.

Surgical Treatment

If the open biopsy demonstrates an invasive cancer (invasive duct or lobular carcinoma), and the lesion can be excised completely (usually less than 4 cm in a normal sized breast), the patient can be considered a good candidate for breast conserving surgery (lumpectomy or local excision, plus axillary dissection for staging Levels I & II), and breast irradiation. In most cases, the surgeons performing the excisional biopsy make an effort to completely excise the tumor which can be examined by the pathologist to ensure that margins are clear.

In patients who have larger tumors, generally over 4-5 cm or centrally located tumors in whom lumpectomy with irradiation would not achieve its desired goal of cosmesis, then modified radical mastectomy (usually with immediate reconstruction), should be considered. In some patients the histology is unfavorable for lumpectomy with irradiation. This would include lesions which have high nuclear grade, diffusely infiltrated to the margin, multifocality, and are associated with an extensive intraductal component.[7] Such patients have a high incidence of local failure, as high as 30%, according to the Joint Center for Radiation Therapy at Harvard. In such cases, a classic modified mastectomy with axillary dissection can be done, usually with immediate reconstruction, if desired by the patient.

Thus, in most cases, a breast conserving or breast preserving procedure (with reconstruction) can be done. This provides an important incentive to the woman to participate in a screening program. She has nothing to lose, certainly not her breast, and everything to gain, possibly early detection of cancer at its most favorable stage, and avoidance of the consequences of presenting with an advanced cancer requiring extensive therapy (frequent event in the past).

Factors Relating to Therapy Selection

The pathology of the primary lesion is a major factor in determining patient management. We have largely discussed the management of an invasive carcinoma, which is the most prevalent lesion. Non-invasive breast cancers, particularly ductal carcinoma in situ (DCIS) (intraductal cancer) , requires special consideration. Since these are generally non-metastasizing, the overall approach is different than in the invasive cancers. Although in the past these patients were commonly treated by mastectomy with or without low axillary dissection, there is a strong interest in treating them in a more selective fashion. In the study on intraductal carcinoma from the NSABP[8] which compared total mastectomy alone with lumpectomy with or without postoperative radiation, there was an overall 14% local recurrence rate. The rate was greater in those who had no postoperative radiation (23% vs 7%) than those with radiation.

Much of the problem with recurrence of DCIS may be related to lesion size. Lagios has pointed out that there is a 21% incidence of occult invasion in patients with a biopsy diagnosis of DCIS and a 32% rate of multicentricity overall.[9] However, among patients with a DCIS lesion size 2.5 cm or less there were no instances of occult invasion, and only 4 out of 25 with multicentricity. In 79 patients with mammographically detected DCIS of 2.5 cm or less, all of which were treated by local excision without radiation or axillary dissection, the local recurrence rate was 10%.[10] Each of these were treated by excision or mastectomy. In 4 patients, the recurrence was in situ cancer detected mammographically. In 4 others, the recurrence was invasive; 3 patients had small invasive cancers of 0.5 cm or less and one patient had a 1.3 cm cancer. It suggests that selecting by size as well as type has an impact. Those that tend not to respond well to local therapy include those whose tumor had poorly differentiated titer, nuclear morphology, or comedo type of coagulation necrosis. In such patients there was a much higher recurrence rate (approaching 19%). In contrast, none of 33 patients with non-necrotic cribriform or micropapillary, well-differentiated DCIS developed a recurrence. This suggests that perhaps well-differenti-

ated micropapillary DCIS may be adequately treated by local excision alone, whereas the comedo type and poorly differentiated type should have additional treatment (radiation and more extensive surgery, possibly mastectomy). This selection process will benefit from future clinical trials.

Breast Conservation

During the last 25 years, breast conservation has been established as an acceptable alternative to breast amputation for women with early breast cancer.[11,12,13] The results of individual experiences in the early 60s led to randomized trials in Europe, the United States and elsewhere.[14,15] All of these studies support the thesis that quandrantectomy, or simply lumpectomy plus radiation has a comparable outcome to radical mastectomy and modified radical mastectomy, which has replaced them in the last decade. Thus, it is fairly clear that women with early breast cancer can participate in therapeutic decision-making, to develop the treatment of choice which best suits their needs. It should be made clear, however, that there are a number of medical, physical and psychological concerns which may influence the decision.

The key to breast conservation therapy is early diagnosis. The opportunity to treat breast cancer successfully without mastectomy is restricted to patients with Stage I and II disease. Lesions under 1 cm have the highest cure rates. To be able to treat lesions under 1 cm requires a program of early detection test done by mammography, although breast self-examination can be helpful.

Radiation Management of Early Breast Cancer

Women with biopsy-proven infiltrating duct carcinoma who choose breast conservation require that the tumor in the breast be excised and should also have an axillary node dissection. Radiotherapy to the breast is added to reduce local recurrence. Based upon the NSABP studies, the node-bearing areas need not be treated prophylactically. A dose of 5,000 cGy to the breast in five to five and one-half weeks is delivered using tangential techniques, which irradiate the breast and pectoralis muscle of the chest wall, attempting to spare the underlying lung as much as possible. A boost of an additional 1,000 cGy in one week is given to those patients in whom the margins of the tumor excision were questionable or frankly positive for residual tumor. The tangential irradiation of the breast is commonly done with a 4 or 6 MV photon beam or cobalt 60 irradiation. For large breasts, a higher photon energy is required in the range of 20-25 MV. The irradiation of the boost area can be accomplished using electron beams of appropriate energy to irradiate the base of the tumor, sparing the underlying lung tissue. Alternatively, a radioactive implant (brachytherapy) can be used to deliver the additional dose.

Axillary node irradiation is generally recommended only for those Stage II patients where tumor cells have broken out of the node into the axillary fat or where the number of positive nodes is greater than 10. When the axilla needs to be irradiated, a dose of 5,000 cGy in 5-6 weeks is given using an irradiation field into this area with the supraclavicular fossa treated contiguously using photon irradiation. For patients with a central or medial lesion and positive axillary nodes, the internal mammary chain may be included in the treatment volume. This area is effectively treated with electrons to a depth of 3 cm.

Ductal carcinoma in situ (DCIS) presents a special problem for therapy. Although it is not actually invasive carcinoma, its natural history is to recur after local excision in 25% of the cases. The recurrences may be invasive carcinoma. Accordingly, mastectomy has been the recommended treatment. There has been a growing experience, however, that wide, local excision and local radiotherapy can be an alternative to mastectomy with salvage mastectomy being offered for the patient with an invasive carcinoma recurrence. For a woman over 50, this probably represents a 5-10% risk over the next 20 years. Most women, given these statistics, will opt for a mastectomy. However, for those who adamantly reject mastectomy, radiotherapy can be employed, provided that careful follow-up of the patient with frequent mammograms can be assured.[16]

The cosmetic effects of breast conservation using radiotherapy generally have been satisfactory.

Lobular carcinoma in situ (LCIS) is probably a histologic subset of DCIS which has been associated with a higher risk of bilaterality. Treatment options for this pathology have ranged from local excision and careful follow-up to mastectomy to bilateral mastectomy. Generally, prophylactic mastectomy and/or bilateral mastectomy are options for women who cannot, psychologically, feel comfortable with a "watch and wait" policy.

The cosmetic effects of breast conservation using radiotherapy generally have been satisfactory. This is of particular importance to the woman who has selected this option. The early pigmentation disappears within a few months. The breast generally becomes somewhat firm and, on occasion, areas of telangiectasia may appear 3 to 4 years post-irradiation. Usually, physicians viewing the breast have a more critical set of criteria than the patient, who is pleased to be able to have her own breast in place without alterations in sensation or overall appearance.

Late Sequelae

Patients who had a radical mastectomy and postoperative radiotherapy in the 1950s and 1960s had a prospect of arm edema, in some series as high as 50-60%. With the modified radical mastectomy and the axillary dissection associated with lumpectomy, the incidence of arm edema is appreciably lower. For the selected Stage II patients who actually receive radiotherapy after an axillary dissection the incidence is now as low as 5-10%.

Depending upon the techniques used, clinically significant radiation

pneumonitis may occur in 1-5% of the patients.[17] Clearly, if efforts are employed to restrict the volume of lung being irradiated, the lower incidence can be expected. If however, large volumes of lung are included in the irradiated field, then significant clinical radiation pneumonitis can occur. These patients will require steroid therapy for weeks to months. Antibiotics and bronchodilators may be required depending upon the clinical course of the illness. Radiation fibrosis, particularly in the apex of the lung, when the supraclavicular fossa is irradiated, is not unusual. However, clinical manifestations of this are rarely seen.

Cardiac damage from irradiation has been reported, particularly pericarditis, which can occur within 4-6 months after irradiation when doses greater than 3,500 cGy to a major section of the pericardium have been delivered.[18] Myocardial damage due to endarteritis and plaque formations leading to coronary artery disease has been reported in patients receiving chest wall irradiation. It is highly unlikely using the tangential techniques currently employed, limiting the irradiation to the chest wall and using electron beam to a depth of 3 cm for the internal mammary chain. In the NSABP B04 trial there did not appear to be an increased risk of cardiac disease for the patients who had radiotherapy, versus the other arms of the study where surgery alone was the treatment.

Radiation is a known carcinogenic. Concern for the irradiated tissues in the contralateral breast which may be at the margin of the irradiated fields has been raised. Surprisingly, this risk for the contralateral breast has not been reported as yet for the thousands of women who have had radiotherapy as part of their breast conservation therapy. Soft tissue sarcomas and osteosarcomas are risks which can occur from 4 years to 20 years after treatment. The probability is difficult to assess, but appears to be exceedingly small, since large series of patients being treated for breast conservation with radiotherapy have now been observed for over a decade without this complication being reported. Acute non-lymphatic leukemia is another related effect of irradiation. However, without adjuvant chemotherapy, women over the age of 50 have no statistically significant increased risk of leukemia. Under the age of 50, a small risk was seen in the earlier NSABP studies.[19]

In a meta analysis of multiple studies done in the 1940-1960 period, women who received postoperative radiotherapy and survived more than 15 years, had a small but significant increase in death rate over those who had not been so treated.[20,21] The exact reason for this is uncertain. One possibility was increased myocardial infarctions in these patients. However, there does not appear to be sufficient data to support this conjecture. This observation will certainly be re-examined for all the women who are currently receiving conservation therapy for breast cancer.

The most serious of all complications is local cancer recurrence after lumpectomy and irradiation. The probability of this is between 5-10% in the decade following treatment for the women who had a complete lumpectomy with clear margins. When the margins are not clear, recurrence rates may be as high as 20%, if boosts are not added to the initial therapy. With the higher doses, the probability of local recurrences falls to the 5-10% range. These patients who fail are candidates for salvage mastectomy, with the prospect that 50% of these women will be disease-free at 10 years.[22]

In the decision of conservation or surgical removal of the breast, per-

Table 1. **Common Adjuvant Chemotherapy Regimens**

CMF–cyclophosphamide, methotrexate and fluorouracil
CMFVP–CMF plus vincristine and prednisone
CMFP–CMF plus tamoxifen
CMFp–CMF plus low dose continuous prednisone
PF–phenylalanine mustard (L-PAM) plus fluorouracil
PFT–PF plus tamoxifen
AC–cyclophosphamide plus adriamycin
CAF–CF plus adriamycin
CAFVP–CAF plus VP
VATH–A plus vinblastine, Thiotepa and Halotestin
PAFT–PFT plus adriamycin
CAFM–CAF plus methotrexate
CNF–CF plus mitoxantrone (Novantrone)

Table 2. **Overview of Clinical Trials**

Approximate Percent Reduction in Mortality at Ten Years		
From CMF-based CHEMOTHERAPY		
	Premenopausal Women	25
	Postmenopausal Women	12
From TAMOXIFEN		
	Premenopausal Women	6
	Postmenopausal Women	19

Table 3. **Prognostic Factors in Breast Cancer**

Accepted	
	TUMOR SIZE
	AXILLARY NODE NUMBER
	RECEPTOR STATUS
	Estrogen
	Progesterone
Promising	
	NUCLEAR GRADE
	FLOW CYTOMETRY
	Ploidy
	DNA synthesis
	LABELLING INDEX
Candidate	
	EGF receptors
	Her-2/Neu oncogene
	Cathepsin D
	P-53 antigen
	Heat shock protein
	Haptoglobin-related protein

haps the most important factor remains the patient's own needs and her selection of the treatment that best fulfills her own psychological requirements. For some women, body image is an overriding consideration and they will resist all efforts and arguments of mastectomy. Other women cannot tolerate the ideas of keeping an organ, even one as important as the breast, that has undergone a malignant change and that is a potential threat to life. For these women, there is no alternative but a thorough mastectomy. Reconstruction of the breast immediately or at a later date is a choice they may make. The important issue is that women now have an opportunity to participate in the therapeutic decision-making, select the treatment option that will allow them to get on with their lives and best heal the psychological scar of this illness.

Systemic Therapy

The systemic management of operable breast cancer is both a complex and dynamic process. It has captivated the interest not only of most physicians, but also women who have had or never have had breast cancer. This is not surprising, given that one in nine women will get breast cancer sometime in her life. Adjuvant therapy is a common term now appreciated by the public, and accepted as a standard form of treatment by most women who have the diagnosis of breast cancer made.

The major interest in adjuvant chemotherapy in the United States began in the early 1970s with the first reports of benefit in node-positive patients using postoperative single agent, L-PAM (l-phenylalanine mustard), by the NSABP,[23] or combination chemotherapy with CMF (cyclophosphamide, methotrexate and fluorouracil) by the Milan group.[24] Actually, this work followed earlier studies of adjuvant therapy by the NSABP which evaluated Thiotepa,[25] and by Cooper et al[26] who had devised a regimen adding VP (vincristine and prednisone) to CMF. The earliest NSABP trial was acknowledged, but infrequently quoted, because only a subset of patients benefited; premenopausal women with positive axillary nodes had an extended disease-free period, but no survival advantage. The Cooper results were initially questioned because they were obtained at a single institution but, ultimately, derivations of the CMFVP program became the standard regimen for three National cooperative groups, Cancer and Leukemia Group B (CALGB), Southwest Oncology Group (SWOG) and Southeast Cancer Study Group (SECSG). CMF was actually devised at the National Cancer Institute before its evaluation in Italy, and presently is the most recognized adjuvant chemotherapy program. Some of the most common adjuvant chemotherapy regimens used today are listed in Table 1.

Tamoxifen (Nolvadex) is an oral antiestrogen and today is probably the most commonly administered adjuvant treatment for women with breast cancer. Clinical trials conducted in Europe have suggested that it is effective, albeit to a different degree, in all women irrespective of their menopausal status, estrogen receptor levels or degree of axillary node involvement.[27,28] Its safety profile, and paucity of side effects, make it an attractive drug to both physicians and patients, but unfortunately not all patients should be treated exclusively with it.

The field of adjuvant therapy has been expanded and become more complex, over the last 15 years. To date, there have been three consensus Development Conferences on this subject held at the National Institutes of Health. The first recommended that adjuvant chemotherapy (CMF) become standard therapy for premenopausal women with node-positive operable breast cancer.[29] The second recommended that tamoxifen become standard therapy for postmenopausal women with positive nodes and positive estrogen receptor primary tumors.[30] The third addressed the issue of treatment in node-negative women, but failed to define a specific cohort who should receive chemotherapy outside the context of a clinical trial.[31] Two overviews, one at 5 years and one at 10 years, have analyzed in aggregate fashion the results of adjuvant CMF and adjuvant tamoxifen trials involving approximately 20,000 and 30,000 women, respectively, treated throughout the world.[32,33] Overall, both treatments are effective. CMF results in a reduction in mortality of 25%, and tamoxifen a reduction of 16%, as noted in Table 2. Despite these advances, there remains considerable controversy

about the optimal treatment for each woman with breast cancer. This is not surprising when one considers the complex nature of the disease and features that may be unique to each individual patient.

Prognostic Factors

Prognostic factors have been studied in an effort to define more fully the unique features of each individual patient with respect to the risks of recurrence and survival. Some of these are listed in Table 3. Three accepted prognostic features most helpful in assessing risk are the presence or absence of axillary nodes, tumor size (diameter) and receptor status (estrogen and progesterone). In the absence of positive axillary nodes, additional, promising assays have been developed to assess risk, using histologic interpretation of nuclear differentiation, or nuclear grade, and flow cytometry to define ploidy (diploid or aneuploid) and the percent of cells undergoing DNA synthesis (S-phase fraction) or, alternatively, determining percent labelled mitoses (PLM) or labelling index by autoradiography as an indicator of proliferative rate. As an example, women with aneuploid tumors and those with a high S-phase fraction have a poorer prognosis in general. There are some logistic and interpretative difficulties with the assays, however. While nuclear grade appears to be a promising prognostic indicator, accepted by some pathologists, others have been unable to reproduce the same interpretation and thus, agree on the classification of a particular specimen. In addition, results from flow cytometric assays are not yet frequently available on most patients and small tumor size precludes their measurement in some others. A variety of other candidate biochemical, immunohistochemical and molecular prognostic factors for recurrence and/or survival are being studied, but presently their unique contributions to defining risk in individual patients remains to be confirmed, and their measurements are not yet readily available to most patients. These include assays for detection of receptors for epidermal growth factor (rEGF), Her-2/Neu oncogene expression or amplification, Cathepsin D level, P-53 expression, heat shock protein (HSP) and haptoglobin-related protein (HRP), among others.[34]

Three issues that frequently generate controversy in breast cancer management are treatment of early breast cancer, therapy of locally-advanced disease, and treatment of the older patient with breast cancer.

Early Breast Cancer

Early breast cancer includes patients with operable Stage I (node-negative) or Stage II (node-positive) disease, when the primary tumor is less than 5 cm in diameter. Considerable controversy exists regarding the role of adjuvant therapy in node-negative women. Should all be treated? Should all receive chemotherapy? Should adriamycin ever be used? Should all receive tamoxifen? How long should treatment be? What indicators of recurrence risk should be used? These are some of the common questions frequently asked and debated today.

Stage I Breast Cancer

Optimal management of women with Stage I breast cancer requires that a full risk assessment be performed, taking into account tumor size and estrogen receptor (ER) status, and DNA content and ploidy if available, before deciding what if any, or what type of, treatment to recommend. Clearly, a woman with a tumor less than 1.0 cm in diameter and with positive ER primary has an excellent prognosis and would be helped only minimally by additional therapy. Women with larger tumors on the other hand, and those with negative ER, have a much greater risk of recurrence and death, so they should be considered for postoperative adjuvant treatment even though their axillary nodes are negative. Their risk of recurrence may be in the range of 25 to 50%, depending upon their individual characteristics. In general, post menopausal women with ER-positive tumors will be initially treated with tamoxifen, and premenopausal patients with an ER-negative primary will be considered for chemotherapy using methotrexate, leucovorin and fluorouracil with or without CMF or other similar programs such as prednisone. Each of these approaches has demonstrated a benefit in reported node-negative trials, with respect to extending the disease-free period, but not overall survival except in certain subsets.[35-38] Beyond this, no firm treatment recommendations can be made and many patients fall in between, in terms of their prognostic features. Formal clinical trials are presently addressing some of these issues, however, including the use of combined chemohormonal therapy, the role of adriamycin, treatment duration and the use of combined hormonal therapies for ER-positive patients.

Stage II Breast Cancer

The management of Stage II breast cancer, like that of Stage I, is constantly undergoing reassessment and investigation in clinical trials conducted throughout the world. As stated, there are conventional treatment recommendations for premenopausal patients with CMF chemotherapy, and tamoxifen for postmenopausal node-positive patients, but clearly better treatment regimens are needed to improve upon the results obtained with these two approaches, particularly in women who have many nodes involved or who have ER-negative and/or progesterone receptor-negative primary tumors. Progesterone receptor level appears to have a stronger correlation with prognosis in node-positive patients, in contrast to its usefulness in Stage I disease, where it adds little to ER status. Adriamycin incorporated into the chemotherapy combination has shown some early promise in a few trials,[39,40] but these results still need to be confirmed in other trials, and the long-term impact of adriamycin needs to be determined. Chemotherapy in postmenopausal patients still needs to be defined, since marginal benefit overall has been seen to date using CMF.[41] The evaluation of adriamycin combinations alone or with tamoxifen, alternating non-cross resistant regi-

mens and vinblastine, adriamycin, thiotepa and halotestin, the sequential use of chemotherapy and tamoxifen, and preoperative chemotherapy is presently in progress, but no firm treatment recommendations can be made outside the context of a clinical trial on any of these programs. In addition, formal programs in autologous bone marrow transplantation have been developed for Stage II patients with an extremely high risk of recurrence and death, such as those with 10 or more nodes involved. Early results of this approach have been promising in selected hands,[42] but the long-term impact and feasibility of this aggressive treatment needs to be defined more conclusively before it becomes standard therapy for any group of women with breast cancer. Recent progress in this approach has been aided by the introduction of hematopoietic colony stimulating factors, which appear to ameliorate some of the toxicities experienced by patients undergoing ablative chemotherapy followed by bone marrow transplantation.

Stage III Locally Advanced Disease

Stage III breast cancer encompasses a heterogeneous group of patients, including those with large (greater than 5 cm in diameter) but operable breast masses with involved or fixed axillary nodes (Stage IIIA) to those (Stage IIIB) with a tumor of any size fixed to the chest wall or skin or with associated inoperable features such as edema, ulceration or satellite skin nodules regardless of axillary node status, or with any internal mammary node involvement. Even though the cancer appears confined to the breast itself, or to the breast and nodes in many cases, this is clearly a systemic condition associated with a poor prognosis when local therapy alone is used. Only one in five patients are alive at 10 years if treated by surgery or radiation alone, or by the combination of both, suggesting that this is a systemic disease at the outset. This has set the stage for the use of combined modality therapy, using surgery, radiation and chemotherapy, in an attempt to control this stage of disease more effectively than has been done in the past.

The median survival of patients with Stage III breast cancer is in the range of 20 to 60 months, varying in different trials and no doubt depending somewhat upon individual features of the cancers studied, but there appears to be some improvement in median disease-free period and survival, since the incorporation of aggressive chemotherapy in the overall treatment schema.[43] Whether this will have a major impact upon the survival at 10 years of patients with non-inflammatory Stage III breast cancer remains to be seen. Impressive results have been seen in patients with inflammatory breast cancer, a universally fatal disease previously, with the use of adriamycin-containing chemotherapy as a component of combined modality therapy, achieving long-term survival in one-third to one-half of patients.[44] Many patients in fact will have no residual cancer pathologically after aggressive induction chemotherapy given preoperatively, or as neoadjuvant chemotherapy with hormonal synchronization, and this in itself is an excellent prognostic factor for an extended disease-free period and improved survival.[45,46]

While most oncologists and surgeons agree that combined modality treatment is necessary, controversy still remains regarding the optimal sequence of local (surgery or radiation) and systemic therapies. This issue will only be resolved through well-controlled prospective clinical trials, which have yet failed to define the optimal sequence. The use of high-dose chemotherapy followed by autologous bone marrow rescue represents another approach not yet fully studied in patients with locally-advanced breast cancer, but some centers are embarking upon these studies in hopes of achieving further gains for women with this stage of disease.

Management of the Older Patient

Breast cancer in the elderly is a complex issue with unique features that extend beyond the individual characteristics of the cancer itself. Age alone impacts considerably upon screening practices, diagnostic testing and treatment patterns of many cancer patients, including women with breast cancer. Age adversely affects survival in breast cancer. Whereas two-thirds of all women diagnosed with breast cancer in their 50s are cured, only one-third of patients over the age of 65 years are cured at present. In Rhode Island, there is no age-stage relationship, meaning that older women do not present with more advanced stage breast cancer than do younger women.[47] All of the reasons contributing to the poorer outcome of older patients with cancer are not known, but certain patterns have become evident. Fewer older women have had a screening mammogram, compared to younger women. Fewer older women have had thorough diagnostic testing once a cancer is detected, compared to younger women.[48] And in Rhode Island, fewer of the elderly have postoperative radiation following conservative surgery for breast cancer, or postoperative systemic therapy compared to younger patients.[49]

There are effective therapies for the older woman, diagnosed with breast cancer, who are treated surgically by mastectomy or a more conservative procedure. The latter mandates postoperative radiation as an adjunctive component in order to optimize local tumor control in the remaining breast and surrounding tissues, unless there are disabling comorbidities that preclude an expected survival of reasonable length. Results with conservative surgery and radiation are equivalent to more extensive surgery in patients with local disease, and this includes the elderly.

Tamoxifen is the systemic treatment of choice for many elderly women with breast cancer.[50] It decreases the number of deaths, reduces distant and bone-only first recurrences, and decreases the number of second breast cancers.[51] Issues of the quality-of-life of older patients are not well characterized in formal clinical trials, but the extended symptom-free time afforded tamoxifen-treated patients no doubt allows these older women to enjoy longer their independence and more

fully such events as their children's and grandchildren's graduations, weddings and other pleasant happenings. The efficacy results noted with tamoxifen lend support to current studies of longer durations of tamoxifen and to future studies comparing it to other tamoxifen-derivatives, such as toremifene, to other hormones, such as newer aromatase inhibitors, or using it in combination with hormones such as fluoxymesterone, or with chemotherapy, as is being done in patients with advanced breast cancer in many trials today. The safety of tamoxifen noted in many clinical trials, and its ability to decrease second or opposite breast cancers, support its current and planned use as a preventive agent in breast cancer.

Chemotherapy for elderly breast cancer patients, or for all postmenopausal patients in fact, is controversial, despite activity of CMF in patients with metastatic disease. CMF is equivalent to but no better than, tamoxifen provided that dose adjustments are made to accommodate the decline in renal function seen with aging.[52] But chemotherapy does represent another treatment option for the elderly who fail tamoxifen or other treatments. Additional agents that can be administered safely to the elderly are definitely needed, as are clinical trials exploring acceptable biologic response modifiers and other molecular-derived growth inhibitory factors.

As we focus in Rhode Island this decade upon the health care of the elderly, through the impetus of the Aging 2000 initiative,[53] we must not lose sight of what is considered optimal treatment of older women with breast cancer. In particular, the older person should not arbitrarily be excluded on the basis of age alone from any diagnostic and therapeutic considerations, since the incidence of breast cancer increases with age and mortality rates need improvement in Rhode Island, throughout the country and the world.

References

1. Henderson IC, Harris JR, Kinne DW, Hellman S. Cancer of the Breast. In: DeVita VT, Jr, Hellman S, Rosenberg SA(eds.) Cancer Principles and Practice of Oncology. JB Lippincott, Philadelphia 1989.
2. Seidman H, Mushinski MH, Gelb SK et al. Probabilities of eventually developing or dying of cancer: United States 1985. CA–A Cancer Journal for Clinicians 35:36-56 (1985).
3. DuPont WD, Page DL. Risk factors for breast cancer in women with proliferative breast disease. N Eng J Med 312:146-151 (1985).
4. Wanebo HJ, Feldman PS, Wilhelm MC, Covell JL, Binns RL. Fine needle aspiration cytology in lieu of open biopsy in the management of breast cancer. Ann Surg 199:569-579 (1984).
5. Laugmuir VK, Cramer SF, Hood ME et al. Fine-needle aspiration cytology in the management of palpable benign and malignant breast disease: Correlation with clinical and mammographic findings. Acta Cytologica 33:93-98 (1988).
6. Hutter R. Role of the pathologist in management of breast cancer. Cancer 66:1363-1372 (1990).
7. Harris JR, Connolly JL, Schnitt SJ et al. The use of pathologic factors in selecting the extent of surgical resection necessary for breast cancer patients treated by primary radiation therapy. Ann Surg 201:164-169 (1985).
8. Fisher ER, Sass R, Ficher B et al. Pathologic findings from the National Surgical Adjuvant Breast Project (Protocol 6): I. Intraductal carcinoma (DCIS) Cancer 57:1197-208 (1986).
9. Lagios MD, Westdahl PR, Margolin FR, Rose, MR. Duct carcinoma in situ. Cancer 50:1309-1314 (1982).
10. Lagios MD, Margolin FR, Westdahl PR, Rose MR. Mammographically detected duct carcinoma in situ. Cancer 63:618-624 (1989).
11. Peters, MV. "Cutting the Gordian knot" in early breast cancer. Ann R Coll Phys Surg Can 8:186 (1975).
12. Pierquin B. Conservative treatment for carcinoma of the breast. Experience of Creteil–Ten year results. In Harris Jr, Hellman S. Silen W (eds.) Conservative Management of Breast Cancer, pp. 11-14. JB Lippincott, Philadelphia (1983).
13. Montague ED, Ames FC, Schell SR, et al. Conservative surgery and irradiation as an alternative to mastectomy in the treatment of clinically favorable breast cancer. Cancer 54:2668 (1984).
14. Veronesi U. Randomized trials comparing conservation techniques with conventional surgery, An overview. In Tobias JS, Peckham MJ (eds.) Primary Management of Breast Cancer: Alternatives to Mastectomy Management of Malignant Disease Series, pp. 131-152. E. Arnold, London 1985.
15. Fisher B, Redmond C, Fisher ER, et al. Ten-year results of a randomized clinical trial comparing radical mastectomy and segmental mastectomy with or without radiation in the treatment of breast cancer. N Engl J Med 312-665 (1985).
16. Harris, JR. ASCO Educational book. pp. 23-33 (1991).
17. Fisher B, Redmond C, Fisher ER, et al. Ten-year results of a randomized clinical trial comparing radical mastectomy and total mastectomy with or without radiation. N Engl J Med 312:674 (1985).
18. Loeffler JS, Goldberg I, Reiser TA, et al. non-invasive cardiac evaluation after definitive radiation therapy for carcinoma of the breast. Proc Am Soc Ther Radiol Oncol 3:1640 (1985).
20. Cuzick S, Peto R, Risher B, et al. Overview of randomized trials of postoperative adjuvant radiotherapy in breast cancer. Cancer Treat Rep 71:15-29 (1987).
21. Cuzick J, Stewart H, Peto R, et al. Cancer Treat Rep 71:7-14, 1987.
22. Harris Jr, Recht A, Amalric R, et al. Time course and prognosis of local recurrence following primary radiation therapy for early breast cancer. J Clin Oncol 2:37 (1984).
23. Fisher B, Carbone P, Economou SG et al. L-Phenylalanine mustard (L-PAM) in the management of primary breast cancer. A report of early findings. N Engl J Med 292:117-122 (1975).
24. Bonadonna G, Brusamolino E, Valagussa P, et al. Combination chemotherapy as an adjuvant treatment in operable breast cancer. N Engl J Med 294:405-410 (1976).
25. Fisher B, Ravdin RG, Ausman RK, et al. Surgical adjuvant chemotherapy in cancer of the breast: Results of a decade of cooperative investigation. Ann Surg 168:337-356 (1968).
26. Cooper RG, Holland JF, Glidewell O. Adjuvant chemotherapy of breast cancer. Cancer 44:793-798 (1979).
27. Nolvadex Adjuvant Trial Organisation. Controlled trial of tamoxifen as a single adjuvant agent in the management of early breast cancer. Br J Cancer June; 57(6):608-11 (1988).
28. Breast Cancer Trials Committee, Scottish Cancer Trials Office (MRC). Adjuvant tamoxifen in the management of operable breast cancer: The Scottish trial. The Lancet ii:171-175 (1987).
29. Moxley JH 3d, Allegra JC, Henney J, Muggia, F. Treatment of primary breast cancer. Summary of the National Institutes of Health Consensus Development Conference. JAMA 1980 Aug 22-29; 244(8): 797-800.

[30] Consensus Conference. Adjuvant chemotherapy for breast cancer. JAMA 254(24): 3461-, (1985).
[31] NIH Consensus Development Conference. Statement on the treatment of early stage breast cancer. Review Article. Oncology (Williston Park) Feb; 5(2):120-4 (1991).
[32] Early Breast Cancer Trialists Collaborative Group. Effects of adjuvant tamoxifen and of cytotoxic therapy on morality in early breast cancer: An overview of 61 randomized trials among 28,896 women. N Engl J Med; 319:1681-92 (1988).
[33] Early Breast Cancer Trialists Collaborative Group. Treatment of Early breast Cancer: Worldwide Evidence in 1985-1990. A Systemic Overview of All Available Randomized Trials in Early Breast Cancer of Adjuvant Endocrine and Cytotoxic Therapy. Oxford University Press, New York, 1990.
[34] McGuire WL, Tandon A, Allred DC, et al. The relative value of tumor size, hormone receptors, flow cytometry, HER-2/Neu oncogene, cathepsin D, and stress response proteins in predicting patient outcome in axillary node negative breast cancer. Presented at NIH Consensus Development Conference on Early Stage Breast Cancer, June 19, 1990.
[35] Fisher B, Costantino J, Redmond C, et al. A randomized clinical trial evaluating tamoxifen in the treatment of patients with node-negative breast cancer who have estrogen-receptor-positive tumors. N Engl J Med 320:479-484 (1989).
[36] Fisher B, Redmond C, Dimitrov NV, et al. A randomized clinical trial evaluating sequential Methotrexate and Fluorouracil in the treatment of patients with node-negative breast cancer who have estrogen-receptor negative tumors. N Engl J Med 320:473-478 (1989).
[37] The Ludwig Breast Cancer Study Group. Prolonged disease-free survival after one course of perioperative adjuvant chemotherapy for node negative breast cancer. N Engl J Med 320:491-496 (1989).
[38] Mansour EG, Gray R, Shatila AH, et al. Efficacy of adjuvant chemotherapy in high-risk node-negative breast cancer. An intergroup study. N Engl J Med 320:485-490 (1989).
[39] Proceedings of the NIH Consensus Development Conference on Adjuvant Chemotherapy and Endocrine Therapy for Breast Cancer. NCI Monographs (Number 1) (1986).
[40] Fisher B, Redmond C, Wickerham DL, et al. Doxorubicin-containing regimens for the treatment of stage II breast cancer: The National Surgical Adjuvant Breast and Bowel Project experience. J Clin Oncol May; 7(5):572-82 (1989).
[41] Taylor, SG IV, Knuiman MW, Sleeper LA, et al. Six-year results of the Eastern Cooperative Oncology Group Trial of observation versus CMFP versus CMFPT in postmenopausal patients with node-positive breast cancer. J Clin Oncol 7:879-889 (1989).
[42] Peters WP, Shpall EJ, Jones RB, et al. High-dose combination cyclophosphamide (CPA), Cisplatin (cDDP) and carmustine (BcNU) with bone marrow support as initial treatment for metastatic breast cancer: Three six-year follow-up. Proceedings of ASCO 9:10 (1990).
[43] Swain, SM. Selection of therapy for Stage III breast cancer. surgical Clinics of North America 5:1061-1079 (1990).
[44] Hortobagyi GN. Comprehensive management of locally advanced breast cancer. Cancer 66:1387-1391 (1990).
[45] Feldman LD, Hortobagyi GN, Buzdar AU, et al. Pathological assessment of response to induction chemotherapy in breast cancer. Cancer Research 46:2578-2581 (1986).
[46] Swain SM, Sorace RA, Bagley CS, et al. Neoadjuvant chemotherapy in the combined modality approach of locally advanced nonmetastatic breast cancer. Cancer Research 47:3889-3894 (1987).
[47] Mor V, Guadagnoli E, Silliman R, et al. Influence of old age, performance status, medical and psychosocial status on management of cancer patients. In Yancik R, and Yates J (eds.) Cancer in the Elderly: Approaches to Early Detection and Treatment, New York, Springer, pp. 127-146 (1989).
[48] Proceedings from the American Cancer Society National Workshop on Cancer Control and the Older Person. Nikko Hotel, Atlanta, Georgia, March 15-16, 1991.
[49] Mor V, Guadagnoli E, Masterson-Allen S, et al. The Brown University Cancer and Aging Study: A Statewide Cooperative Investigation. Rhode Island Medical Journal 71:379-386 (1988).
[50] Cummings FJ, Gray R, Davis TE, et al. Adjuvant tamoxifen treatment of elderly women with Stage II breast cancer: A double blind comparison with placebo. Ann Int Med 103:324-29 (1985).
[51] Cummings FJ, Eudey L, Gray R, et al. Adjuvant tamoxifen vs placebo in elderly women with node-positive breast cancer: Long-term follow-up and causes of death. Proc Am Soc Clin Oncol 10:(719) (1991).
[52] Taylor, SG IV, Gelman RS, Falkson G, et al. Combination chemotherapy vs tamoxifen as initial therapy of stage IV breast cancer in elderly women. Ann Int Med 104:455-461 (1985).
[53] Magaziner IC, Aging 2000: Pursuing progressive care for Rhode Island's elderly. Rhode Island Med J 74 (June, 1991); 295-298.

★ ★ ★ ★ ★ ★ ★ ★ ★ ★ ★ ★ ★ ★ ★ ★ ★

Rural Health ★ ★
CARING
for the country

★ ★ ★ ★ ★ ★ ★ ★ ★ ★ ★ ★ ★ ★ ★ ★ ★

National Rural Health Association
15th Annual Conference on Rural Health
May 6–9, 1992
Hyatt Regency Crystal City
Washington, DC

ONLY ONE H_2-ANTAGONIST HEALS REFLUX ESOPHAGITIS AT DUODENAL ULCER DOSAGE. ONLY ONE.

Of all the H_2-receptor antagonists, only Axid heals and relieves reflux esophagitis at its standard duodenal ulcer dosage. Axid, **150** mg b.i.d., relieves heartburn in **86%** of patients after one day and **93%** after one week.[1]

AXID®
nizatidine
150 mg b.i.d.

ACID TESTED. PATIENT PROVEN.

1 Data on file, Lilly Research Laboratories. *See accompanying page for prescribing information*

© 1991, ELI LILLY AND COMPANY

NZ-2947-B-249304

AXID®

nizatidine capsules

Brief Summary. Consult the package insert for complete prescribing information.

Indications and Usage: 1. *Active duodenal ulcer*—for up to 8 weeks of treatment at a dosage of 300 mg h.s. or 150 mg b.i.d. Most patients heal within 4 weeks.

2. *Maintenance therapy*—for healed duodenal ulcer patients at a dosage of 150 mg h.s. at bedtime. The consequences of therapy with Axid for longer than 1 year are not known.

3. *Gastroesophageal reflux disease (GERD)*—for up to 12 weeks of treatment of endoscopically diagnosed esophagitis, including erosive and ulcerative esophagitis, and associated heartburn at a dosage of 150 mg b.i.d.

Contraindication: Known hypersensitivity to the drug. Because cross sensitivity in this class of compounds has been observed, H_2-receptor antagonists, including Axid, should not be administered to patients with a history of hypersensitivity to other H_2-receptor antagonists.

Precautions: *General*—1. Symptomatic response to nizatidine therapy does not preclude the presence of gastric malignancy.

2. Dosage should be reduced in patients with moderate to severe renal insufficiency.

3. In patients with normal renal function and uncomplicated hepatic dysfunction, the disposition of nizatidine is similar to that in normal subjects.

Laboratory Tests—False-positive tests for urobilinogen with Multistix® may occur during therapy.

Drug Interactions—No interactions have been observed with theophylline, chlordiazepoxide, lorazepam, lidocaine, phenytoin, and warfarin. Axid does not inhibit the cytochrome P-450 enzyme system; therefore, drug interactions mediated by inhibition of hepatic metabolism are not expected to occur. In patients given very high doses (3,900 mg) of aspirin daily, increased serum salicylate levels were seen when nizatidine, 150 mg b.i.d., was administered concurrently.

Carcinogenesis, Mutagenesis, Impairment of Fertility—A 2-year oral carcinogenicity study in rats with doses as high as 500 mg/kg/day (about 80 times the recommended daily therapeutic dose) showed no evidence of a carcinogenic effect. There was a dose-related increase in the density of enterochromaffin-like (ECL) cells in the gastric oxyntic mucosa. In a 2-year study in mice, there was no evidence of a carcinogenic effect in male mice, although hyperplastic nodules of the liver were increased in the high-dose males as compared with placebo. Female mice given the high dose of Axid (2,000 mg/kg/day, about 330 times the human dose) showed marginally statistically significant increases in hepatic carcinoma and hepatic nodular hyperplasia with no numerical increase seen in any of the other dose groups. The rate of hepatic carcinoma in the high-dose animals was within the historical control limits seen for the strain of mice used. The female mice were given a dose larger than the maximum tolerated dose, as indicated by excessive (30%) weight decrement as compared with concurrent controls and evidence of mild liver injury (transaminase elevations). The occurrence of a marginal finding at high dose only in animals given an excessive and somewhat hepatotoxic dose, with no evidence of a carcinogenic effect in rats, male mice, and female mice (given up to 360 mg/kg/day, about 60 times the human dose), and a negative mutagenicity battery are not considered evidence of a carcinogenic potential for Axid.

Axid was not mutagenic in a battery of tests performed to evaluate its potential genetic toxicity, including bacterial mutation tests, unscheduled DNA synthesis, sister chromatid exchange, mouse lymphoma assay, chromosome aberration tests, and a micronucleus test.

In a 2-generation, perinatal and postnatal fertility study in rats, doses of nizatidine up to 650 mg/kg/day produced no adverse effects on the reproductive performance of parental animals or their progeny.

Pregnancy—Teratogenic Effects—Pregnancy Category C—Oral reproduction studies in rats at doses up to 300 times the human dose and in Dutch Belted rabbits at doses up to 55 times the human dose revealed no evidence of impaired fertility or teratogenic effect; but, at a dose equivalent to 300 times the human dose, treated rabbits had abortions, decreased number of live fetuses, and depressed fetal weights. On intravenous administration to pregnant New Zealand White rabbits, nizatidine at 20 mg/kg produced cardiac enlargement, coarctation of the aortic arch, and cutaneous edema in 1 fetus, and at 50 mg/kg, it produced ventricular anomaly, distended abdomen, spina bifida, hydrocephaly, and enlarged heart in 1 fetus. There are, however, no adequate and well-controlled studies in pregnant women. It is also not known whether nizatidine can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. Nizatidine should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nursing Mothers—Studies in lactating women have shown that 0.1% of an oral dose is secreted in human milk in proportion to plasma concentrations. Because of growth depression in pups reared by treated lactating rats, a decision should be made whether to discontinue nursing or the drug, taking into account the importance of the drug to the mother.

Pediatric Use—Safety and effectiveness in children have not been established.

Use in Elderly Patients—Healing rates in elderly patients were similar to those in younger age groups as were the rates of adverse events and laboratory test abnormalities. Age alone may not be an important factor in the disposition of nizatidine. Elderly patients may have reduced renal function.

Adverse Reactions: Worldwide, controlled clinical trials included over 6,000 patients given nizatidine in studies of varying durations. Placebo-controlled trials in the United States and Canada included over 2,600 patients given nizatidine and over 1,700 given placebo. Among the adverse events in these placebo-controlled trials, only anemia (0.2% vs 0%) and urticaria (0.5% vs 0.1%) were significantly more common in the nizatidine group. Of the adverse events that occurred at a frequency of 1% or more, there was no statistically significant difference between Axid and placebo in the incidence of any of these events (see package insert for complete information).

A variety of less common events were also reported; it was not possible to determine whether these were caused by nizatidine.

Hepatic—Hepatocellular injury (elevated liver enzyme tests or alkaline phosphatase) possibly or probably related to nizatidine occurred in some patients. In some cases, there was marked elevation (>500 IU/L) in SGOT or SGPT and, in a single instance, SGPT was >2,000 IU/L. The incidence of elevated liver enzymes overall and elevations of up to 3 times the upper limit of normal, however, did not significantly differ from that in placebo patients. All abnormalities were reversible after discontinuation of Axid. Since market introduction, hepatitis and jaundice have been reported. Rare cases of cholestatic or mixed hepatocellular and cholestatic injury with jaundice have been reported with reversal of the abnormalities after discontinuation of Axid.

Cardiovascular—In clinical pharmacology studies, short episodes of asymptomatic ventricular tachycardia occurred in 2 individuals administered Axid and in 3 untreated subjects.

CNS—Rare cases of reversible mental confusion have been reported.

Endocrine—Clinical pharmacology studies and controlled clinical trials showed no evidence of antiandrogenic activity due to nizatidine. Impotence and decreased libido were reported with similar frequency by patients on nizatidine and those on placebo. Gynecomastia has been reported rarely.

Hematologic—Anemia was reported significantly more frequently in nizatidine than in placebo-treated patients. Fatal thrombocytopenia was reported in a patient treated with nizatidine and another H_2-receptor antagonist. This patient had previously experienced thrombocytopenia while taking other drugs. Rare cases of thrombocytopenic purpura have been reported.

Integumental—Urticaria was reported significantly more frequently in nizatidine- than in placebo-treated patients. Rash and exfoliative dermatitis were also reported.

Hypersensitivity—As with other H_2-receptor antagonists, rare cases of anaphylaxis following nizatidine administration have been reported. Rare episodes of hypersensitivity reactions (eg, bronchospasm, laryngeal edema, rash, and eosinophilia) have been reported.

Other—Hyperuricemia unassociated with gout or nephrolithiasis was reported. Eosinophilia, fever, and nausea related to nizatidine have been reported.

Overdosage: Overdoses of Axid have been reported rarely. If overdosage occurs, activated charcoal, emesis, or lavage should be considered along with clinical monitoring and supportive therapy. The ability of hemodialysis to remove nizatidine from the body has not been conclusively demonstrated; however, due to its large volume of distribution, nizatidine is not expected to be efficiently removed from the body by this method.

PV 2093 AMP [101591]

Additional information available to the profession on request.

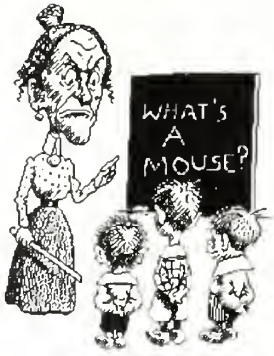
Lilly

Eli Lilly and Company
Indianapolis, Indiana
46285

NZ-2947-B-249304

c 1991, ELI LILLY AND COMPANY

Computer Lessons



Computers don't have to be complicated or expensive. Scrooge Macdoc® is a Macintosh based office management system for the solo practitioner that tracks income, and prints forms and bills at the click of a button. Designed by a Doctor to be used by Doctors, it is simple and powerful, but costs less than 1/2 the price of comparable systems!

Don't get a hard sell when you buy medical software. The only way to judge software is to use it in your office. With Scrooge Macdoc® there is a no-risk trial period, and a 30 day money-back guarantee.

Don't buy hardware that has a name you don't recognize. Some companies will sell you an expensive computer system that has inexpensive hardware which was made in a country you haven't heard of since 6th grade geography class. Scrooge Macdoc® runs on Macintosh computers that are incredibly simple to use, extremely reliable, and made in America.

Know the price before someone walks in the door. Scrooge Macdoc® software costs $2,700. If you don't already own a Macintosh, the hardware cost is $4,000. Total system cost is $6,700 which may be leased over 3 years for $240/month with a $1 buyout.

For information or a demonstration contact:

David A. Lowe, M.D.
615 Jefferson Blvd
Warwick, RI 02886
738-6865 or 884-2410

Class dismissed!

HEALTH BY NUMBERS

Rhode Island
Department of Health
Barbara A. DeBuono, MD, MPH
Director of Health

Breast Cancer Screening among Low-Income Hispanic Women in Rhode Island

In Rhode Island Hispanic women of low income are less likely to be screened for breast cancer than other low income women. In a recent survey of Rhode Island women ages 40 and over who reside in minority low-income census tracts (low income areas with at least 5% Black or Hispanic population), Hispanic women were far less likely than non-Hispanic women to have been screened according to current guidelines, or to have received mammography alone according to current guidelines (Figure 1).

Current Guidelines for Breast Cancer Screening, Women Ages 40 and Over

Women ages 40-49:
Physical Breast exam every year
Mammography every 2 years

Women ages 50 and over:
Physical breast exam every year
Mammography every year

Compared to other women, Hispanics had distinct health beliefs about breast cancer and breast cancer screening, which may account for their low utilization of the latter. Although they were just as likely as others to believe that mammography is effective for revealing early breast cancer, and were almost as likely to believe in its safety, they were far less likely to believe themselves susceptible to breast cancer, and were far more likely to believe in its incurability (Figure 2). It is possible that the latter combination of beliefs may have inhibited screening. Why be screened if one is not susceptible, or indeed if the disease is incurable.

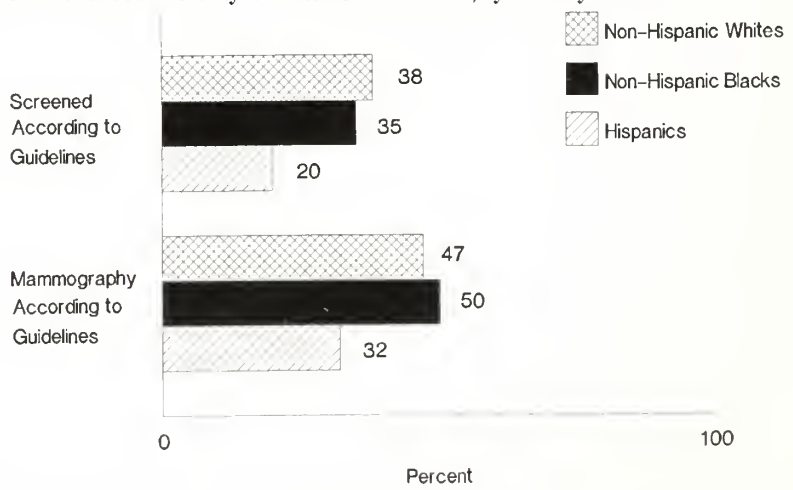
Low-income Hispanic women were distinct from other low-income women in other ways. They were far less likely than others to have completed high school or to have family incomes exceeding 200% of the federal poverty level (Table 1). They were less likely to utilize providers for general medical or gynecological care. They were also less likely to have received a Pap test or to have performed breast self-examination in the past year. In short, barriers to breast cancer screening appear to be formidable in this population.

Hispanics have been chosen as the subject of "special population objectives" in *Healthy People 2000*, the recently published "National Health Promotion and Disease Prevention Objectives" for the US. Among "Objectives Targeting Hispanics" is one which reads "Increase to at least 80% the proportion of Hispanic women aged 40 and older who have ever received a clinical breast examination and a mammogram, and to at least 60% those aged 50 and older who have received them within the preceding 1 to 2 years".[1] The Rhode Island Department of Health will attempt to achieve this objective among low-income Hispanic women in our state, laying the groundwork with a grant from the National Cancer Institute for promoting "breast and cervical cancer screening among poor and minority women."

[1]US Public Health Service. Healthy People 2000. National Health Promotion and Disease Prevention Objectives. US Government Printing Office, Washington, DC, 1991.

Preparation of this report was supported in part by a grant to the Rhode Island Department of Health from the National Cancer Institute (R01-CA52958; Dr Judith P. Feldman, Principal Investigator).

Figure 1. **Proportion of women screened for breast cancer according to current guidelines, and with mammography alone according to current guidelines, Rhode Island, 1991, sample of women who reside in minority low-income census tracts, by ethnicity and race**



Submitted by the Rhode Island Cancer Registry, John P. Fulton, PhD, Administrator. Health by Numbers *is edited by Jay S. Buechner, PhD, and William J. Waters, Jr., PhD.*

Figure 2. **Proportion of women who perceived their susceptibility to breast cancer as high, the seriousness of breast cancer as high, the effectiveness of mammography as high, and the safety of mammography as high, Rhode Island 1991, sample of women who reside in minority low-income census tracts, by ethnicity and race.**

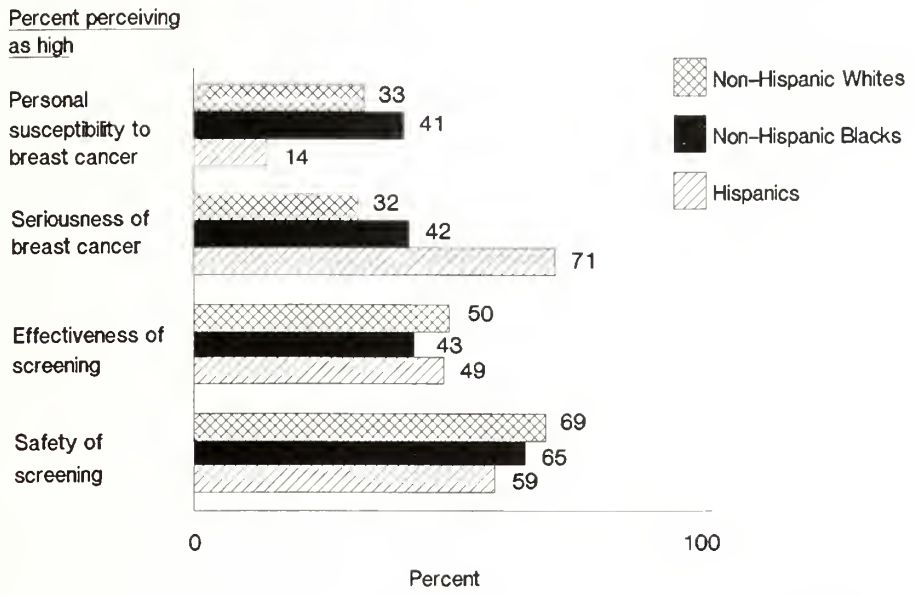


Table 1. **Percentage of Women 40 Years of Age and Over, Categorized by Sociodemographics and Medical Care Utilization, Rhode Island 1991, Sample of Women who Reside in Minority Low-Income Census Tracts by Ethnicity and Race.**

Sociodemographics and Utilization	Percentage Non-Hispanic White (N=489)	Non-Hispanic Black (N=156)	Hispanic (N=118)
Sociodemographics			
Age 40-69	40%	63%	71%
HS diploma received	65	75	32
Income equal to or above 200% of poverty level	38	38	5
Have any health insurance	96	92	82
Currently married	44	45	51
Utilization			
Have regular provider for gen med care	85	82	64
Visited provider for gen med care in previous year	86	85	77
Have regular source of gynecological care	85	93	85
Visited any provider for gyn care in previous year	49	55	42
Screening mammogram ever recommended by a provider	65	60	48
Pap test received in previous year	45	49	39
Self breast exam performed in previous year	65	71	56

Source: Survey of Rhode Island women ages 40 and over who reside in minority low-income census tracts, 1991, Rhode Island Department of Health

You treated little Johnny for measles in kindergarten, chicken pox in 3rd grade, mono in high school.

But what can you do for his HIV today?

People with HIV are special patients with specific needs. That's why it helps to have experience with HIV when treating an infected patient–the kind of experience doctors find at Clinical Partners.

Clinical Partners is a group of healthcare professionals dedicated to helping patients live with HIV. We are alone in the complete array of services we provide to physicians, employers and insurers of those living with HIV. Our early intervention averts costly hospital stays, while increasing patient care and support.

Operating successfully in Boston, New York and Los Angeles, Clinical Partners is pleased to announce the first anniversary of our Providence office, under the expert guidance of Linda Durand NP, RNC and Deborah Matson CISW, MSW.

We want Rhode Island physicians to know Clinical Partners is here to help, and here to stay. As the patient's primary physician, you can benefit from our knowledge and experience, which is available to help you treat HIV infection and AIDS.

To find out how Clinical Partners can be your partner in treating HIV patients, call our Providence office today at 454-8880 or 1-800-285-8880.

ClinicalPartners

Helping people make choices about HIV.

RIMS
Insurance Brokerage Corporation

Insurance Professionals serving Health Care Professionals.

We do it better!

- Because our purpose is to serve RI doctors and allied health care professionals.
- Because our staff has 15 years of solid experience in medical liability underwriting.
- Because our board of directors is composed predominately of doctors with the same problems, stresses and concerns as you.
- Because we support political action in matters of health care benefiting all Rhode Islanders.
- Because our bottom line is superior service.

Phone 272-1050 — ask for Shirley and
Learn How We Can Do It Better For You!

RIMS Insurance Brokerage Corporation
The Experts in Medical Liability Insurance

Now offering up to 2M/4M limits for select insureds.

Also offering workers' compensation.

RIMS INSURANCE BROKERAGE CORPORATION

RIMS Insurance Brokerage Corporation
One Hayes Street, Providence, Rhode Island 02908
Phone (401) 272-1050 FAX (401) 272-1051

Are your investments as successful as you are?

If your hard work and success have allowed you to build a portfolio of $250,000 or more, we'd like to work with you.

account administrator who will act as your personal financial advisor and you'll be backed by a team of investment managers with a history of proven investment success.

{ Professionally Managed Investments }

Because at Citizens Bank, our Trust and Investment Management team can provide you with the exceptional service, experience, and performance that will help you get the most from your investments. You'll have an

To put us to work for you call Malcolm Starr at 456-7445. Because there's never been a better time for Citizens.

Trust and Investment Management Services

CITIZENS BANK

Citizens Trust Company/Citizens Savings Bank

The Differential Diagnosis of Premenstrual Syndrome

Marguerite Vigliani, MD, FACOG

Premenstrual symptoms were not recognized as a clinically relevant problem until the early part of the 20th century.

As a woman and a practicing obstetrician/gynecologist, I see a number of patients weekly wanting an evaluation for premenstrual syndrome, or PMS. Usually these patients state that they have been to other doctors and are now coming to me specifically because I am female. Indeed, the lay press has devoted considerable attention to premenstrual syndrome and the notion that this is a specific endocrine disorder which is best treated by a sympathetic female physician.

An Historical Overview of PMS

Premenstrual symptoms were not recognized as a clinically relevant medical problem until the early part of the 20th century. Menarche was uncommon before age 14 or 15, menopause occurred at age 35 to 40, and women usually spent the intervening years either pregnant or lactating. For PMS symptoms many unusual remedies were tried, including offerings to deities, blistering baths, isolation, leeching, emetics, purges, bleeding, mesmerism, and herbs.[1,2]

Marguerite Vigliani, MD, FACOG, is Director, Division of Gynecology, Roger Williams Medical Center and Clinical Assistant Professor of Obstetrics and Gynecology, Brown University and Women and Infants Hospital, Providence, Rhode Island.

In 1931, Frank[3] proposed that premenstrual tension was due to estrogenic activity in the blood. Subsequently, Israel[4] suggested that the unopposed estrogen effect described by Frank was due to deficient progesterone production. However, the idea of premenstrual syndrome as an endocrine disease, or more specifically a progesterone responsive disease, was popularized by Katherine Dalton, a British physician who began publishing papers in the early 1950s describing cases of premenstrual asthma, epilepsy, and migraine, all of which responded successfully to treatment with progesterone.[5,6] Although many other physicians used progesterone for premenstrual tension, very few achieved the excellent results obtained by Dalton.[7-14]

In 1980, Dalton's theory achieved notoriety when she became an expert witness in the successful defense of three young female convicts who were imprisoned for repeated criminal acts ranging from theft to murder.[15] "Diminished responsibility" due to PMS was successfully pleaded in all three cases. These cases are excerpted below:

Case 1. A 28-year-old nulliparous worker in the food industry, who had had epilepsy from infancy until the age of 14, was in custody on a charge of manslaughter. Her menarche was at the age of 15, and since the age of 16 she had received twenty-six convictions; offences included causing criminal damage, theft, trespassing, writing threatening letters, possessing a dangerous weapon, and finally, a fatal stabbing. While in detention her episodes of disturbed behavior included arson, attempted escape, hanging, strangling, drowning, smashing windows, cutting her wrists and assault.

The patient said she became confused and suddenly angry with a longing for alcohol during the last two premenstrual days. A psychiatrist reported: "Most of the time she is pleasant and cooperative but at times she loses her senses and can be quite impulsive". She was receiving Ativan (lorazepam) 5 mg thrice daily. Treatment with injections of progesterone

ABBREVIATIONS USED:
ACOG: American College of Obstetricians and Gynecologists
CT: computerized tomography
EEG: electro encephalogram
FSH: follicle stimulating hormone
IUD: intrauterine device
LH: luteinizing hormone
MAO: monamine oxidase
PMS: premenstrual syndrome
PTU: propylthiouracil

50 mg intramuscularly daily cured her irritability and confusion but she remained depressed premenstrually. For the past 9 months she has received 100 mg progesterone daily and no other drugs; she has become calm, rational, and is able to concentrate. There have been no more episodes of disturbed behavior and she is now on probation for 3 years.

Case II. An 18-year-old nulliparous student, whose menarche was at 13 years, had no behavior problems until she was 14-1/2 years old when she made her first suicide attempt. The next year her parents noticed several episodes of bizarre behavior, which were always during the paramenstruum; these included swallowing weedkiller, running away from home, shaving her head and eyebrows, cutting her face, and alcohol intoxication. She set fire to her home and was sent to prison where, during the next three paramenstruums, she attempted arson, cut her wrists, and tried to strangle herself. Treatment with dydrogesterone 10 mg twice daily eased her premenstrual tension but not the premenstrual depression or violence. She was then given progesterone injections 100 mg daily from mid-cycle until menstruation and had no further episodes of bizarre behavior. She was freed on probation for 2 years and has had excellent health on progesterone. She now has a full-time managerial job, is married, and has had no further episodes of disturbed behavior in the past 22 months.

Case III. A 19-year-old unemployed nulliparous woman had her menarche at the age of 16. The next year she began to display criminal behavior at monthly intervals for which she was initially given probation, later Borstal training, and then prison sentences, but offences continued even during detention. Offences during the last 2 premenstrual days and the first 2 days of menstruation including making false 999 calls, criminal damage, assaults on police, hanging attempts, arson, threats to kill her grandmother, and slashed wrists. She said that during premenstrual days she became irritable, depressed, violent, and felt like 'walking out of life'. She claimed she had often asked for help during the paramenstruum when she felt a sudden urge to jump out of the window or assault someone. This was confirmed by a prison officer's statement which said 'feels she will smash up. Doesn't want to leave prison', and a report from Borstal which said: 'she sometimes asked to be put in a cell alone as she felt safe there'.

Monthly episodes of bizarre behavior continued despite fortnightly injections of flupenthixol 20 mg, chlorpromazine 50 mg thrice daily, and orphenadrine 50 mg twice daily. Daily injections of progesterone 50 mg from midcycle to menstruation were started and her other treatment was gradually stopped. She lost her violent urges and felt calmer.

On release from prison her injections were, unfortunately, not resumed for 7 days during which she committed another offence. She was taken in to custody and 3 weeks later she alerted the staff at the hostel that she felt violent. The next day, before injections could be obtained, she threw a knife at a man, escaped from the hostel, made a false 999 call, and assaulted 3 policewomen. She received a 2 year prison sentence during which her unpredictable episodes of violence in the paramenstruum were again noticed. Five months later she resumed progesterone therapy, and she has been well behaved for the last 4 months in prison.[15]

Unfortunately, Dalton's diagnosis was made on the basis of history alone and was not supported by physical examination or laboratory data. Dalton has treated hundreds of criminals at her Premenstrual Syndrome Clinic at University College in London. She publishes voluminously,[16-19] as does her American counterpart, Roland V. Norris,[20] who is the director of numerous free-standing clinics in the US which distribute natural progesterone for PMS. Nevertheless despite much research, none of the controlled, double-blind studies show a benefit for natural progesterone in the treatment of PMS when compared to placebo.[21-26]

Because of the conflicting and inconclusive results of these studies, many other causes have been postulated to explain the etiology of PMS. These include estrogen excess, altered estrogen and progesterone ration, prolactin excess, Vitamin B-6 deficiency, hormone allergy, fluid retention, reactive hypoglycemia, endorphin withdrawal, and other aberrations in the cyclic functions of the hypothalamic-pituitary axis. Although there have been many attempts to demonstrate endocrinological differences between PMS patients and controls, there have not been any consistently significant differences demonstrated between the hormones of PMS patients and controls.[27-40]

The primary care physician is . . . sometimes faced with a demanding patient who arrives in the office with a preset notion of what her diagnosis is and what therapy she wants.

Studies of menstrual cycle-related changes in levels of estradiol, progesterone, follicle-stimulating hormone (FSH), luteinizing hormone (LH), DHEA-S, testosterone, estradiol-binding globulin, dihydrotestosterone, prolactin, and cortisol show no significant diagnosis-related effects between patients with premenstrual syndrome and control subjects. In addition, no significant diagnosis-related difference have been found when mean plasma progesterone levels have been compared. Patients did have significantly lower testosterone levels than controls.

The Hormones of the Normal Menstrual Cycle

The normal menstrual cycle is characterized by a follicular and a luteal phase. The pre-ovulatory or follicular phase starts at the end of menses. Numerous primordial follicles in the ovary compete to become the dominant follicle under the influence of the pituitary hormones and local steroids in the ovary. The follicle which is destined to become the dominant follicle produces a large amount of

Table 1. **Changes Found in PMS**

Physical	Affective	Perception, cognition, behavior
Change in sleep patterns	Feelings of well-being	Difficulty thinking in a rational way
Worsening of sinus symptoms	Excitement	Forgetfulness
Irritated eyes	Increased sexual drive	Hypersensitivity to sounds, sight and touch
Difficulty using contact lenses	Heightened creativity	Stimulus overload
Reduction of hearing or temporary deafness	Feelings of intimacy	Clumsiness
Mouth sores, ulcers and dryness	Bursts of increased energy	Difficulty with fine movements
Bleeding from the nose	Irritability, anger, aggressive feelings	Increased risk of accidents (in home, industry, motor vehicle)
Acne	Paranoid ideation	
Darkness under the eyes	Depression (can be severe, with suicidal feelings)	
Swelling and tenderness of the breasts	Tension (like a stretched wire about to snap)	
Breathlessness	Frequent mood changes	
Feeling of suffocation	Feeling unhappy (nothing makes the patient feel good)	
Palpitations	Feelings of and fear of losing control	
Rapid heartbeat	Crying spells	
Crushing chest pain	Feeling overstimulated and oversensitive and feeling guilty about feelings, behavior and interactions with others	
Worsening of asthma symptoms	Obsessive compulsive behavior	
Bloating of the abdomen		
Constipation or diarrhea		
Pelvic heaviness		
Rectal pressure		
Feeling of pressure in the bladder		
Need to pass urine more frequently, urgency		
Easy bruising and welting of skin		
Itching and burning of skin (especially face, hands, abdomen, genital area)		
Hair falling out		
Muscle weakness, aching and cramping		
Pain, swelling and stiffness of joints (especially hands, shoulders, knees, ankles)		
Backache		
Craving for sweets, sweet foods, chocolate or just for more food in general		
A sense of internal shaking		
Swings between a feeling of being energetic and of being fatigued		

Derived from Labrum (42).

estrogen which in turn stimulates the pituitary gland in positive feedback. As a result, the dominant follicle grows progressively larger until it ruptures and releases the egg. The high systemic levels of estrogen in the periovulatory period are associated with a number of side effects such as bloating, weight gain, breast tenderness, and increased mucus production.

After ovulation, the follicular granulosa cells increase in size and undergo a process known as luteinization. The resulting corpus luteum is responsible for production of progesterone which functions to relax uterine smooth muscle, modulate tubal motility, and thickens cervical mucus. Systemically, these symptoms associated with the luteal hormones are similar to the symptom normally associated with pregnancy; breast tenderness, bloating, fluid retention, constipation, and so on. A number of women also report emotional or cognitive changes during the luteal phase of the cycle. Generally these include increased irritability and/or depression (see Table 1).[42]

For the majority of women, the physical and emotional changes which take place during the menstrual cycle are tolerated and perceived as minor. However, there is a distinct minority of women who find themselves markedly disabled by symptoms. Yet, there are no biochemical ways of distinguishing patients with PMS from normal women. Dalton herself admits that it is impossible to demonstrate a progesterone deficiency in patients as compared to controls and argues that the reason is that progesterone is secreted in a pulsatile fashion. In 1986, she presented a paper at the National ACOG meeting in defense of progesterone therapy, citing numerous reasons why controlled prospective studies of progesterone therapy could not be performed.[43]

Despite her attempts at legitimacy, Dalton's work has been rejected by the scientific community. An increasing number of outraged patients have banded together in local and national self-help groups to advocate and politicize progesterone therapy for PMS. An entire PMS subculture has developed, fueled by the media and consisting of women who demand treatment, expensive clinics that provide such treatment, pharmacists who supply progesterone, and organized boosters,

which sell pamphlets and "information" on PMS. These groups allege that the medical community has rejected Dalton's work because of sexism and male chauvinism. PMS Action, which advertises for both lay people and professionals, is one of the more militant of these organizations whose major function is to recruit "PMS sufferers" and instruct them in demanding progesterone.

The primary care physician is thus sometimes faced with a demanding patient who arrives in the office with a preset notion of what her diagnosis is and what therapy she wants. As pointed out by Reid,[44] it is not surprising that many physicians feel intimidated by this kind of patient, especially in view of reports of increased premenstrual suicide rates and psychiatric admissions.[45]

Differential Diagnosis

Ultimately, the decision as to whether the diagnosis is a chronic psychiatric disorder with a premenstrual increase in symptoms or a premenstrual affective syndrome is a matter of clinical judgement which should be made by the primary care physician. The differential diagnosis should be made in the usual manner, via a complete history and physical exam. The history must include a list of current symptoms and also a review of any past medical illnesses, an account of any previous hospitalizations, a review of any medications the patient may be taking, including over-the-counter drugs and vitamins. It is important to take a nutritional history and to determine the extent of the patient's use of nicotine, alcohol, and other recreational drugs. A history of alcohol or substance abuse by the patient or other family members is very important. The patient's habits must be reviewed with particular reference to sleep habits, eating habits, bowel habits, sexual activities, and exercise.

A meticulous menstrual history is necessary; at what age the patient's periods began, what her periods are like, whether they are different presently from the way they were previously, when they changed, whether or not she skips periods, how heavy and long her periods are , whether or not she has ever used any contraceptive, and what kind. It is also necessary to know if she had any pregnancies and how they went, how difficult it was for her to get pregnant, whether or not there were any complications, how she felt about her pregnancies, how she perceives her children, how she feels about any abortions or miscarriages, whether or not she is aware of any wetness or discharge at mid-cycle, what premenstrual symptoms she consistently has, and the history of these symptoms over her lifetime. If there are menstrual difficulties at the present time, more details should be obtained from the patient. A review of symptoms must be done and inquiry must be made about family history, social history sexual history, and psychiatric history. A complete physical examination must also be performed.

On the basis of history and physical examination the physician must make a diagnosis and establish a problem list. Whenever necessary, supporting data should be obtained form the laboratory. Frequently, the differential will include a variety of psychiatric diagnoses, all of which may have exacerbations premenstrually. Depression, anxiety disorders, schizophrenia, and borderline personality disorders have been known to worsen premenstrually. In addition, there are a number of clues that can be derived from the field of neurochemistry on changes observed in the menstrual cycle, though the mechanism has not been well worked out.

Neurochemistry Associated with the Menstrual Cycle

Monoamine oxidase (MAO), one of the major catabolic enzymes of the central nervous system degrades epinephrine and norepinephrine to metabolites. MAO can be measured in plasma and has been shown to vary with the menstrual cycle,[46] being low just before ovulation and high premenstrually. There is also some evidence that estrogen can inhibit MAO activity and thus enhance central norepinephrine, leading to elevation of mood in the first half of the cycle. In the second half of the cycle, MAO activity is not inhibited and peripheral levels are also higher; thus the decreased adrenergic tone could be responsible for decreased moods or depression.[47]

Additionally, it is known that estrogen metabolites, the catechol estrogens, compete with each other for the enzymes tyrosine hydroxylase and catechol O-methyltransferase.[48] Both of these activities further enhance central norepinephrine and decrease its catabolism.

For the majority of women, the physical and emotional changes which take place during the menstrual cycle are tolerated and perceived as minor.

Finally there is evidence that there are changes in receptor sensitivity which correlate with cyclical variations in gonadal steroid levels. With respect to adrenergic receptors, alpha 2 adrenergic binding has been reported to vary with changes in estrogen levels.[49] High doses of estrogen have been shown to produce down regulation of beta receptors and to increase serotonin sensitivity.[50] Serotonin turnover has been shown to be increased by progesterone in the luteal phase of the menstrual cycle.[51] Also, it has been demonstrated that there is decreased serotonin uptake in the luteal phase of the menstrual cycle in women with premenstrual depression symptoms.[52]

Thus, it can be seen that estrogen and progesterone modulate the central nervous system tone by having an effect on the metabolism of the transmitters and the sensitivity of receptors. From the individual's point of view, the biochemical changes which take place in the central and peripheral nervous systems over the course of the menstrual cycle have a profound influence upon a woman's perception of herself and her environment, with enhanced nociperception being the rule in the premenstruum.

For many illnesses, symptoms may be mild and not interfere with normal function except during the premenstruum, when patients become aware of nonspecific symptoms. They may fail to report these symptoms or be unaware of their chronicity. They may find it more socially acceptable to think of their problem as a premenstrual phenomenon rather than a generalized disorder.

Physicians must see through the media hype and recognize PMS as a chief complaint rather than a disease and use differential diagnosis to find the underlying causes.

Patients with organic illnesses, sometimes of major proportions, may tolerate their symptoms quite well during the first half of the cycle but become incapacitated during the premenstruum, causing them to seek medical attention. The primary care physician must remember that PMS patients are convinced that they have a "chemical imbalance" and that a majority of them are seeking pharmacological relief of their symptoms. Careful evaluation of these patients can be very rewarding. In 1988, I reported three cases of women with life-threatening illnesses who presented with a chief complaint of PMS.[53] These, and two additional cases, are summarized below:

Case 1. A 43-year-old hypertensive white female was first seen for routine gynecological care in February of 1982. She recently lost both parents, divorced an alcoholic husband, moved out of state, and started a new job. She had a new boyfriend and was contemplating pregnancy, but had an IUD in place. Initial evaluation revealed fibrocystic breast disease, a mildly abnormal Pap smear, and a mitral valve murmur. She underwent mammography, colposcopy, and was referred to a cardiologist who confirmed the diagnosis of mitral regurgitation.

One year later she had a nontender inguinal mass. She was treated with ten days of antibiotics, and the mass resolved. Three months later she complained of premenstrual fatigue, nervousness, and irritability. Because of multiple life stresses, she was referred for counseling without a medical workup. After visiting several specialists for a variety of complaints, she was admitted to a local hospital for subacute endocarditis. She received 6 weeks of intravenous antibiotics and underwent surgery for mycotic aneurysms.

Case 2. A 47-year-old white female was seen because of premenstrual nervousness, agitation, mood swings, anxiety, weakness, lethargy, and fatigue. These symptms had been present for approximately two years. In the months prior to consultation, she had experienced an exacerbation of symptoms, which she had attributed to the "flu." She stated that her family physician had prescribed erythromycin by phone, but that she had developed an allergic reaction to it, including hives, eczema, bloating, and difficulty breathing. She apparently responded to benadryl with partial resolution of her symptoms, but stated that she could not differentiate the symptoms of PMS from those that she attributed to the flu. Her physical exam showed nothing more than a mild degree of obesity and a cyst in the upper outer quadrant of the left breast, which had been present for several years.

After the initial consultation but before her next visit, she was admitted to a nearby hospital with progressive respiratory distress, initially thought to be pneumonia. She rapidly developed cyanosis and cardiac arrest. She was resuscitated, but could not be weaned from a ventilator. She underwent a lung biopsy which showed idiopathic pulmonary fibrosis, and she expired on the fifth hospital day. An autopsy confirmed the diagnosis of idiopathic pulmonary fibrosis.

Case 3. A 51-year-old white female was seen because of tiredness and loss of energy that seemed to coincide with her menstrual cycle. She had recently developed oligomenorrhea and hot flashes and wondered whether her complaints represented premenstrual or menopausal symptoms She was a one-pack-a-day smoker and had a negative medical history except for pneumonia. Results of the physical examination were unremarkable, except for some atrophic genital changes. Blood chemistry and thyroid function tests were within normal limits. A complete blood count showed a mild normocytic normochromic anemia, and the Westergren sedimentation rate was elevated to 60 mm at 1 hour. Because the patient was a smoker, chest x-ray was ordered. This showed a right hilar density. The patient underwent a bronchoscopy and a CT scan which confirmed a diagnosis of lung cancer. She underwent a right lobectomy, which showed adenocarcinoma. Five years later, she is alive and shows no evidence of cancer.

Case 4. A 42-year-old white female presented with "constant" PMS symptoms. The patient stated that she rarely felt well and was bothered by bloating irritability, nausea, exhaustion, sleepiness, and headache. Her menses had always been irregular, occurring every 2-6 weeks with a heavy flow on the first day. She was using a diaphragm for contraception and had recently been married. Her social history was rather complex. There was an illegal abortion at age 17, problems now in parenting 2 adolescent stepchildren, marijuana use, and a recent job change. General and pelvic examinations were unremarkable. Her LH and FSH levels were normal, as well as her progesterone level, which showed evidence of ovulation. The prolactin level was normal. The liver function tests were mildly elevated, as was the Westergren sedimentation rate. A T4 was 21 (normal range 4.5-11.5), and a T3 resin uptake was 53 (normal range 35-45). Diagnosis of hyperthyroidism was confirmed by a neuroendocrinologist and a thyroid scan. The patient's symptoms improved with inderal. She subsequently elected to be treated with PTU and is currently free of symptoms on PTU, 50 mg three times daily.

Case 5. A 29-year-old nulligravida was seen for polymenorrhea, dysmenorrhea, mittelschmerz, and severe premenstrual symptoms. The pa-

tient stated that at the time of ovulation and continuing right through the menses, she became disoriented, depressed, weepy, and had severe abdominal pain and bloating. She complained of anxiety attacks which consisted of hot flashes, palpitations, and numbness. Each attack lasted about 20 minutes and she felt completely disabled afterward. She stated that these attacks occurred anytime during the cycle, but were generally premenstrual and were interfering with her career.

Physical examination was unremarkable. A basal body temperature chart showed a biphasic 25-day cycle with ovulation occurring on Day 10 and symptoms beginning from Day 16 to Day 19 and lasting until menses occurred. Her blood work was unremarkable, but an EEG confirmed the diagnosis of temporal lobe epilepsy. The patient is currently free of symptoms on phenobarbitol, 15 mg three times a day.

These five cases, like many other in my practice, illustrate the importance of careful evaluation of patients presenting with premenstrual complaints. Even in the absence of specific life-threatening medical problems the history and physical examination can reveal a diagnosis.

Frequently, the problem is a dysfunctional family or alcohol-related. In my own practice, I have often found PMS patients to be alcoholics, spouses of alcoholics, or the adult children of alcoholic parents.

Case 6. The patient was a 42-year-old white female who complained of absent sexual desire, anorgasmia, insomnia, and premenstrual syndrome. She stated that prior to her periods, she became severely depressed, had suicidal ideation, and would have killed herself if not for the fact that it would hurt other people. At the time of her evaluation, she was living with her second husband after a separation and an unsuccessful. attempt at divorce. She was estranged from her two grown children and had recently lost her job. Her memories of childhood were unhappy, characterized by a father who was difficult to please and a mother who was frequently absent because of work. The fifth of six children, she experienced much sibling rivalry. An unplanned pregnancy at age 20 prompted her first marriage which lasted 10 years. After her first two children, she had a series of extramarital affairs, which ultimately resulted in the dissolution of the marriage. During that time she had a miscarriage and terminated three pregnancies, one of which was her husband's. She was also hospitalized for a major depressive episode, but left against medical advice after three days. She continued in psychotherapy for two and a half years, however, and continued on anti-depressive medication for several months. Her second marriage lasted the same amount of time, but was not complicated by pregnancy as her husband had had a vasectomy. She had extramarital affairs. She admitted to drinking a half gallon of whisky per week and smoking 2 packs of cigarettes per day. She also took an indeterminate amount of Xanax for anxiety. Her general physical and pelvic examinations were unremarkable. Tests showed a macrocytic anemia and her serum glutamic-oxaloacetic transaminase (SGOT) was slightly elevated. A diagnosis of alcoholism was made with possible underlying depression and a question or borderline personality. The patient was referred for further evaluation and she is currently at an inpatient psychiatric hospital for alcohol detoxification.

Investigators have also noted that alcohol appears to be a factor in 40-50% of cases.[54,55] Another concomitant problem is abuse by a spouse or roommate or a history of incest. The abuse, current or past, can be physical or verbal and can involve the patient's children as well.

Case 7. The patient is a 43-year-old white female with a chief complaint of premenstrual syndrome. She stated that one week prior to her menses she became emotional, easily upset, and depressed. Her menses were regular every 30 days, lasting 3 days with a light flow. She was using rhythm and spermicides for contraception, but was requesting permanent sterilization because her husband would not use a condom and her fear of pregnancy was resulting in such infrequent relations and sexual dysfunction that both partners were dissatisfied. This was a second marriage for both. Her husband was older and had grown children from a previous marriage. His ex-wife was homeless and psychotic. He had undergone a vasectomy in the previous marriage and a reversal in this marriage. The patient now felt that she did not want to have any children because in addition to the sexual problems, there was also frequent quarreling, excessive use of alcohol by both partners, and many episodes of family violence, the most recent episode requiring police intervention.

Physical examination of the patient was unremarkable except for extensive bruising of the upper arm with resolving hematoma. The patient was advised not to have sterilization at this point; she was reassured that her premenstrual symptoms were probably rational and physiological; and she was referred to AA, Al-Anon, a woman's shelter, a psychiatrist, and family court.

In most cases, the PMS patient is the abused party. Psychological studies of PMS patients have in fact shown these women to be generally passive introverted, submissive, and unassertive.[56] It is possible that it is actually suppressed anger at an intolerable home situation which is exploding premenstrually under the influence of the hormones of ovulation.

My approach in these cases has been to offer psychological support, validation, and to invite the PMS patient to explore this intriguing hypothesis through further counseling. When psychiatric illness, organic illness, and family discord have all been ruled out, the problem may be psychological. Although the patient may not have any psychiatric illness per se, there may be some unresolved psychological issue or issues which resurface each month after ovulation. A meticulous obstetri-

cal and contraceptive history may be necessary to elucidate the etiology of the patient's unresolved reproductive conflicts.

Case 8. The patient was a 32-year-old white female who had been followed at a PMS clinic for several years prior to consulting me. She had been taking progesterone by suppository, 400 mg four times a day from Day 10-27 for one year without much improvement of her PMS symptoms. These symptoms were mainly emotional. She characterized herself as moody and irritable, and her relationships with others were characterized by aggressiveness. There were many unresolved conflicts with her mother. When asked, she stated that she believed she had had PMS since childhood. Her recollection of childhood was that she was very moody and had very few friends. She suffered from a great deal of remorse and depression as a result of her aggressive behavior. She also had a great deal of guilt about a termination of pregnancy which had occurred in 1978 and her decision to marry a man who had had a vasectomy. The differential diagnosis was felt to include characterological depression versus situational depression, and this was discussed with the patient. She was advised to wean off the progesterone and either seek counselling or keep an introspective diary which she would review with me at the time of her next visit. She elected the latter course, and at the time of her next visit was markedly improved. She had stopped the progesterone and had had many sessions with her husband. When seen one year later, she was free of PMS symptoms other than minor bloating.

Case 9. A 32-year-old nulligravida white female was seen for PMS. She stated that her mood was very erratic a few days before her period. She experience free floating rage, was prone to anger and was very depressed and anxious; she also had bloating and water retention. Her menses were previously every 27 days, but recently had become more frequent, occurring every 21-24 days. She had a moderate flow with occasional clotting. She stated that she had always had a "sunny" disposition until her problem with PMS. Her only previous experience with depression was four years earlier when she had a brief course of psychotherapy because of depression associated with a job decision. The patient had been married for 8 years. At the time of the marriage, both had decided they did not want children, so the husband underwent a permanent sterilization. The premenstrual symptoms started three years after the marriage began. The patient admitted to some ambivalence, which she had harbored for the past 1-2 years about her husband's sterilization. Her general physical exam was unremarkable. Pelvic exam showed fibroids; blood chemistries were within normal limits except for mildly elevated prolactin level. The patient elected a trial of low dose Parlodol, but could not tolerate this due to side effects. Subsequently after much discussion and counseling, she and her husband decided to have a vasectomy reversal done. She had a miscarriage approximately 8 months later, but was essentially without premenstrual complaints, and 2 years later delivered a viable newborn infant.

Discussion

The cases presented illustrate the importance of careful evaluation of patients who present with premenstrual complaints. Cases 1,2, and 3 make it clear that a medical problem of major proportions may be obscured by the patient's interpretation of her own symptoms. Cases 4 and 5 show that the complaints of change in personality, emotional instability, weakness, or tiredness should be taken seriously and a search for metabolic or endocrinological abnormalities should be attempted despite the patient's self-diagnosis. Cases 6,7,8 and 9 show that even when there is no organic illness present, a differential diagnosis and problem list can help the patient immensely.

The majority of patients do not have a single underlying medical or psychological problem, but present with a combination of factors. A PMS patient may relate a history of multiple stresses, poor health habits, use of a variety of drugs, and a combination of alcohol, nicotine, and caffeine. Frequently, there are reproductive conflicts or conflicts with a spouse or roommate which account for a great deal of anger. Often the intensity of the patient's symptoms will wax and wane depending upon the stresses which are present in her life, and also depending upon the degree to which she lacks control over other life events. For example, symptoms are commonly exacerbated at times of illness in the family or financial problems.

Each case is unique as each person is unique. I feel that with every patient's premenstrual syndrome, the opportunity arises for the physician to find an underlying problem, and sometimes to unravel severe forms of social disorganization or personal confusion which are not recognized by the patient but are displaced onto a diagnosis of PMS. This self-diagnosis places the blame for these seemingly insoluble problems on to the woman herself, and further increases her feelings of powerlessness to make changes in her life.

All patients should have a full medical and social history taken. Very often, women learn as much about themselves during the taking of the history as the physician does, and thus the opportunity for intervention arises. During the history and physical examination, as well as in subsequent visits, patients should be advised to follow an appropriate diet, which is high in fiber and vegetables and low in fat and cholesterol. The patient should cut down on or eliminate salt, coffee, tea, cola, chocolate, and alcohol. All patients should be advised of the benefits of a regular exercise program, weight loss, smoking cessation, good sleep habits, bowel habits, and rest. Stress relaxation techniques should be reviewed and the patient should be given an opportunity to improve her overall health habits before her next visit. In the meantime, she should be expected to keep track of her symptoms, perhaps with the aid of a basal body temperature chart if there is a question of hormone imbalance, and she should be instructed to keep some

sort of an introspective diary of episodes which provoke symptoms. When appropriate, marital counseling, personal counseling, or alcohol or drug counseling should be recommended.

In any event, it is important that whatever the diagnosis or problem list, the physician should accept the patient's diagnosis of PMS and work with her on a problem list. It serves no purpose to antagonize the patient by telling her that she does not have PMS or that there is no such thing as PMS. Occasionally vitamin therapy, valium, prostaglandin inhibitors, or diuretics may alleviate some specific symptoms or have a placebo effect; suppression of the ovarian cycle with oral contraceptives, androgens, or danazol may also be effective; however, the patient must be made to understand that premenstrual syndrome is not a single disease entity with a single cure.

With respect to progesterone, there is not one shred of scientific evidence that progesterone is any more effective than a placebo in treating premenstrual complaints. Progesterone is produced in excess after ovulation, and is responsible for most of the premenstrual symptoms that are normally called "molimina". When administered in its natural form, it can be expected to be rapidly converted by the body to estrogen and other steroid hormones. If given in high enough doses, the side effects that one would expect would be the same as those experienced when an excess of estrogen is administered.

There are indeed some women who have progesterone lack because of defective ovulation. This condition, known as corpus luteum defect, can be documented in a variety of ways, but any doctor who gives a woman a prescription for natural progesterone on the basis of her self-diagnosis of premenstrual syndrome without any documentation of a progesterone lack and without any investigation of her symptoms is failing to perform the role of a physician. Any woman who seeks and finds this type of medical care bears some of the responsibility for untoward effects of this self-prescribed treatment.

PMS has been heavily promoted by the media, and women have learned to "believe in" the disease, perhaps because of the belief that they are a defective species. The media allege that most doctors, who are men treating a "woman's " disease, don't take women seriously; indeed, the "raging hormones" hypothesis still appeals to many male chauvinists as an explanation of society's ills. The pharmaceutical industry and the proprietary trades have followed the lead of the media and have embarked upon a vast marketing campaign to sell drugs to women for PMS relief. Physicians must see through the media hype and recognize PMS as a chief complaint rather than a disease and use differential diagnosis to find the underlying causes.

References

1. Henriksen, E. The Melancholia of Menstruation or Premenstrual Tension. Clinical Obstetrics and Gynecology 1962;5:252.
2. Rose RM, Abplanalp JM. The Premenstrual Syndrome. Hospital Practice 1983.
3. Frank RT. The Hormonal Causes of Premenstrual Tension. Archives of Neural Psychiatry 1931; 26:1053.
4. Israel SL. Premenstrual Tension. JAMA 1931; 110:1721.
5. Greene R, Dalton K. The Premenstrual Syndrome. British Medical Journal 1953; 1:1007.
6. Dalton K. Similarity of Symptomatology of Premenstrual Syndrome and Toxemia of Pregnancy and Their Response to Progesterone. British Medical Journal 1954; 2:1071.
7. Gray LA. The Use of Progesterone in Nervous Tension States. Southern Medical Journal 1941; 34:1004.
8. Rees L. The Premenstrual Tension Syndrome and Its Treatment. British Medical Journal 1953; 1:1014.
9. Mukerjee C. Premenstrual Tension: A Critical Study of the Syndrome. Journal of Independent Medical Association 1954; 24:81.
10. Parker AS. The Premenstrual Tension Syndrome. Medical Clinical of North America 1960; 44:339.
11. Waxman D. Progesterone and Premenstrual Tension Syndrome. British Medical Journal 1968; 4:188.
12. Sacher EJ, ed. Topics in Psychoendocrinology. Greene and Stratton, new York 1975, pp. 19-58,,, chapter titled "Mood and Menstrual Cycle" by Smith SL.
13. Smith SL. The Menstrual Cycle and Mood Disturbance. Clinical Obstetrics and Gynecology 1976; 19:391.
14. Sampson GA. Premenstrual Syndrome: A Double-Blind Controlled Trial of Progesterone and Placebo. British Journal of Psychiatrics 1979; 135:209.
15. Dalton K. Cyclical Criminal Acts in Premenstrual Syndrome. The Lancet 1980; 2(8203):1070-1071.
16. Dalton K. The Premenstrual Syndrome. Heinemann Medical Books, London, 1964.
17. Dalton K. Premenstrual Syndrome and Oral Progesterone Therapy. Heinemann Medical Books, London, 1977.
18. Dalton K. A Guide to Premenstrual Syndrome an its Treatment. London, 1981.
19. Dalton K. Once a Month. Second edition, Hunter House Inc., Publishers, Claremont, CA 1979.
20. Norris RV. Progesterone for Premenstrual Tension. Journal of Reproductive Medicine 1983; 28:509-516.
21. Reid RL, Yen SSC. Premenstrual Syndrome. American Journal of Obstetrics and Gynecology 1981; 139:85.
22. Maddocks S, Hahn P, Moller F, et al. A Double-Blind Placebo Controlled Trial of Progesterone Vaginal Suppositories in the Treatment of Premenstrual Syndrome. American Journal of Obstetrics and Gynecology 1986; 154:573.
23. Dennerstein L, Spencer-Gardner C, Gotts G, et al. Progesterone and the Premenstrual Syndrome: A Double Blind Crossover Trial. British Medical Journal 1985; 290:1617.
24. Magos A, Studd J. Progesterone and the Premenstrual Syndrome: A Double Blind Crossover Trial. British Medical Journal 1985; 291:213.
25. Andersch B, Hahn L. Progesterone Treatment of Premenstrual tension: A Double Blind Study. Journal of Psychosomatic Research 1989; 29:489.
26. Maddocks S, Hahn P, Muller F, Reid RL. A double Blind Placebo-Controlled Trial of Progesterone Vaginal Suppositories in the Treatment of Premenstrual Syndrome. American Journal of Obstetrics and Gynecology 1986; 154:573.
27. Backstrom T, Cartensen H. Estrogen and Progesterone in Relation to Premenstrual Tension. Journal of Steroid Biochemical 1974; 5:257.
28. Backstrom T, Mattson B. Correlation of Symptoms in Premenstrual Tension to Oestrogen and Progesterone Concentrations in Blood Plasma. Neuropychobiology 1975; 1:80.
29. Backstrom T, Wide L, Sodergard R, et al. FSH, LH, TeBG capacity estrogen, and progesterone in women with premenstrual tension during the luteal phase. Journal of Steroid Biochemistry 1976; 7:473.
30. Halbreich W, Assael M, Ben-David M, Bornstein R. Serum prolactin in women with premenstrual syndrome. the Lancet 1976; 2:654.
31. Mundy MR, Brusch MG, Taylor RW. Progesterone and aldosterone levels in premenstrual tension syndrome. Journal of Endocrinology 1977; 73:219.

[32] Mundy M. Hormone levels in severe premenstrual tension. Current Med Res Opinion 1985; 4:16.

[33] Taylor JW. Plasma progesterone, oestradiol, and premenstrual symptoms. Acta Psychiatric Scand 1979; 60:76.

[34] Andersch B, Abrahamson L, Wenderstrom C, et al. Hormone profile in premenstrual tension: Effects of bromocrytine and diuretics. Clinical Endocrinology 1979; 11:659.

[35] O'Brien P, Selby C, Symonds EM. Progesterone, fluid, and electrolytes in premenstrual syndrome. British Medical Journal 1:1161.

[36] Mundy MR, Brusch MG, Taylor RW. Correlations between progesterone, oestradiol, and aldosterone levels in premenstrual syndrome. Clinical Endocrinology 1981; 14:1.

[37] Crutchley M et al, eds. Advances in Neurology. Raven Press, New York, 1982, pp. 215-216, chapter entitled "Menstrual Headache" by Nattero G.

[38] O'Brien P, Symonds EM. Prolactin levels in premenstrual syndrome. British Journal of Obstetrics and Gynecology 1982; 89:306.

[39] Backstrom T, Sanders D, Leaks R. Mood, sexual hormones and the menstrual cycle.

[40]. Rubinow DR, Roy-Byrne PP. Premenstrual syndromes: Overview from a methodological perspective. American Journal of Psychiatry 1984; 141:163.

[41] Rubinow DR, Hoban MC, Grover GN, et al. changes in plasma hormones across the menstrual cycle in patients with menstrually elated mood disorder and in controlled subjects. Am J Ob/Gyn 1988; 158:5-11.

[42] Labrum MB. Hypothalamic, Pineal and Pituitary Factors in the Premenstrual Syndrome. J Reprod Med 1983; 28(7):438-445.

[43] Dalton K. PMS as an Endocrine Disease. (read at the meeting of ACOG, Chicago, Sept 18, 1987)

[44] Reid RL. Premenstrual Syndrome: A Time for Introspection. Am J Ob/Gyn 1986; 155(5):921-926.

[45] Janowsky DS, Gorney R, et al. Premenstrual-menstrual increases in psychiatric hospital admission rates. Am J Ob/Gyn 1969; 103(2):189-191.

[46] Usdin E, ed. Neuropsychoplasmacology of Monoamines and Their Regulatory Enzymes. Raven Press, New York, 1974: chapter by Youdin ME, Holzbauer M, Woods HF, entitled "Physiochemical properties, development and regulation of central and peripheral monoamine oxide activity."

[47] Klaiber EL, Kobayashi U, Broverman DM, et al. Plasma monoamine oxidase activity in regularly menstruating women and in amenorrheic women receiving cyclic treatment with estrogens and a progestin. J Clin Endocrin Metab 1971; 33:630.

[48] Lloyd T, Weisz J. Direct inhibition of tyrosine hydroxylase activity by catechol estrogens. J Biol Chem 1978; 253:4481.

[49] Roberta JM, Goldfine R, Tsuchiya AM, et al. Estrogen treatment decreases alpha-adrenergic binding sites on rabbit platelets. Endocrinology 1979; 104:722.

[50] Biegon A, Reches A, Snyder L, et al. Serotoninergic and noradrenergic receptors in the rate brain: Modulation by chronic exposure to ovarian hormones. Life Sc 1983; 32:2015.

[51] Costa S, Gessa GL, Sandler M, eds. Advances in Biochemical Pharmacology. Raven Press, New York, 1974, vol 10, pp. 273, chapter by Ladisich W, entitled "Progesterone influences on regional metabolism in the rat brain."

[52] Ho BT, ed. Serotonin in Biological Psychiatry. Raven Press, New York, 1974, chapter titled "Serotonin levels and platelet uptake during premenstrual tension," by Taylor D, Mathew RJ, Ho BT, et al.

[53] Vigliani M. PMS: Symptom or diagnosis. J Am Med Women's Association 1988; 43(6):181-182.

[54] Price WA, DiMazio LR, Eckert JL. Correlation between PMS and alcoholism among women. Ohio Med 1987; 83(3):201-202.

[55] Halliday A, Bush B, Cleary P, Aronson M, Delbanco T. Alcohol Abuse in Women Seeking Gynecological Care.

[56] Keye WR, Hammond DC, Strong T. Medical and psychological characteristics of women presenting with premenstrual symptoms. Ob and Gyn 1986; 68 (5):634-637.

Address correspondence to:
Marguerite Vigliani, MD
461 Maple Avenue
Barrington, RI 02806

YOCON®
YOHIMBINE HCl

Description: Yohimbine is a 3a-15a-20B-17a-hydroxy Yohimbine-16a-carboxylic acid methyl ester. The alkaloid is found in Rubaceae and related trees. Also in Rauwolfia Serpentina (L) Benth. Yohimbine is an indolalkylamine alkaloid with chemical similarity to reserpine. It is a crystalline powder, odorless. Each compressed tablet contains (1/12 gr.) 5.4 mg of Yohimbine Hydrochloride.

Action: Yohimbine blocks presynaptic alpha-2 adrenergic receptors. Its action on peripheral blood vessels resembles that of reserpine, though it is weaker and of short duration. Yohimbine's peripheral autonomic nervous system effect is to increase parasympathetic (cholinergic) and decrease sympathetic (adrenergic) activity. It is to be noted that in male sexual performance, erection is linked to cholinergic activity and to alpha-2 adrenergic blockade which may theoretically result in increased penile inflow, decreased penile outflow or both.

Yohimbine exerts a stimulating action on the mood and may increase anxiety. Such actions have not been adequately studied or related to dosage although they appear to require high doses of the drug. Yohimbine has a mild anti-diuretic action, probably via stimulation of hypothalmic centers and release of posterior pituitary hormone.

Reportedly, Yohimbine exerts no significant influence on cardiac stimulation and other effects mediated by B-adrenergic receptors. Its effect on blood pressure, if any, would be to lower it; however no adequate studies are at hand to quantitate this effect in terms of Yohimbine dosage.

Indications: Yocon® is indicated as a sympathicolytic and mydriatric. It may have activity as an aphrodisiac.

Contraindications: Renal diseases, and patient's sensitive to the drug. In view of the limited and inadequate information at hand, no precise tabulation can be offered of additional contraindications.

Warning: Generally, this drug is not proposed for use in females and certainly must not be used during pregnancy. Neither is this drug proposed for use in pediatric, geriatric or cardio-renal patients with gastric or duodenal ulcer history. Nor should it be used in conjunction with mood-modifying drugs such as antidepressants, or in psychiatric patients in general.

Adverse Reactions: Yohimbine readily penetrates the (CNS) and produces a complex pattern of responses in lower doses than required to produce peripheral a-adrenergic blockade. These include, anti-diuresis, a general picture of central excitation including elevation of blood pressure and heart rate, increased motor activity, irritability and tremor. Sweating, nausea and vomiting are common after parenteral administration of the drug.[1,2] Also dizziness, headache, skin flushing reported when used orally.[1,3]

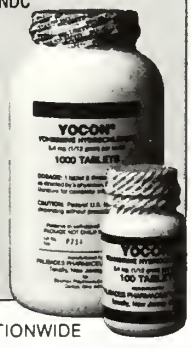
Dosage and Administration: Experimental dosage reported in treatment of erectile impotence.[1,3,4] 1 tablet (5.4 mg) 3 times a day, to adult males taken orally. Occasional side effects reported with this dosage are nausea, dizziness or nervousness. In the event of side effects dosage to be reduced to ½ tablet 3 times a day, followed by gradual increases to 1 tablet 3 times a day. Reported therapy not more than 10 weeks.[3]

How Supplied: Oral tablets of Yocon® 1/12 gr. 5.4 mg in bottles of 100's NDC 53159-001-01 and 1000's NDC 53159-001-10.

References:

1. A. Morales et al., New England Journal of Medicine: 1221. November 12, 1981.
2. Goodman, Gilman — The Pharmacological basis of Therapeutics 6th ed., p. 176-188. McMillan December Rev. 1/85.
3. Weekly Urological Clinical letter, 27:2, July 4, 1983.
4. A. Morales et al., The Journal of Urology 128: 45-47, 1982.

Rev. 1/85



AVAILABLE AT PHARMACIES NATIONWIDE

PALISADES PHARMACEUTICALS, INC.
219 County Road
Tenafly, New Jersey 07670
(201) 569-8502
1-800-237-9083

YOUR SPECIALTY IS WORTH AN EXTRA $8,000 A YEAR.

If you're a resident in any of the following specialties:

- anesthesiology
- orthopedic surgery
- general surgery
- neurosurgery
- colon/rectal surgery
- cardiac/thoracic surgery
- pediatric surgery
- peripheral/vascular surgery
- plastic surgery

you could be eligible for an $8,000 annual stipend in the Army Reserve's Specialized Training Assistance Program.

You'll also be using your skills in a variety of challenging settings, from major medical centers to field hospitals, and there are opportunities for conferences and continuing education.

We know your time is valuable, so we'll be flexible about the time you serve. Your immediate commitment could be as little as two weeks a year, with a small added obligation later on. If you'd like to talk to an Army Reserve physician, or if you'd like more information about the stipend program or other medical opportunities, call our experienced Army Reserve Medical Counselor:

CAPTAIN JOHN GRIMES
203-624-5325

BE ALL YOU CAN BE.®
ARMY RESERVE

OBGYN LIBRARY AVAILABLE

"Obstetrics/Gynecology"
1954-1991

"American Journal of Obstetrics/Gynecology"
1951-1988

"Clinical Obstetrics and Gynecology"
1958-1988

"OBGYN Survey" - 1967-1990

For more information call
521-4471

Rx C3: Coughs, Colds, Flu . . .

S-T FORTE™

SUGAR FREE

NDC #0372-0005-16

Hydrocodone Bitartrate 2.50 mg./5 ml.;
(Warning: May be habit forming.)
Phenylephrine & Phenylpropanolamine Hcl. āā 5 mg./5 ml.; Pheniramine Maleate 13.33 mg./5 ml.; Guiafenesin 80 mg./5 ml. & 5% Alcohol by volume.

Rx C3—Same formula with sugar.
S-T Forte Syrup NDC #0372-0004-16
Complete information in the package.

(401) 942-8555
Toll Free 1-800-638-SCOT

TM: Scot-Tussin Pharmacal Co., Inc.
Cranston, R.I. 02920-0217

NURSING PLACEMENT HOME CARE INC.

"The 1st Choice in Certified Home Health Agencies"

We Are Proud To Announce:

NURSING PLACEMENT HOME CARE, INC.,
a **MEDICARE** and **MEDICAID CERTIFIED AGENCY.**

NPHC, the only letters that define Quality and Dependable Home Health Care in RI. Your patients deserve a choice and **NPHC** can offer them that – with a complete range of care options from Home Health Aides to Registered Nurses and all therapies.

We have provided your hospitals and private patients with quality care for 15 years and are now certified to serve all homebound patients in Rhode Island.

- RN assessments
- 24 hr. supervision
- RN
- HHA
- PT
- OT
- Speech
- MSW
- IV Therapy
- Pediatrics

"For Home Care You Can Rely On"

NPHC

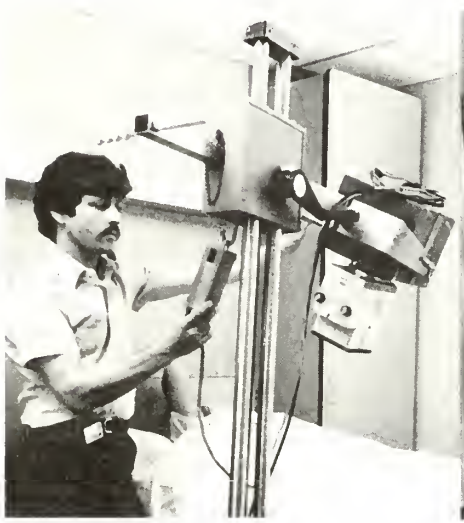
Please call 453-4474
1-800-287-2940

There's more to Portable X-Ray Service than X-Rays.

Yes, our main business is to provide you with fast, efficient, diagnostic X-Ray services, but we have much more to offer . . . including a staff of people who really care.

- Diagnostic X-Ray Services
- EKG
- Holter-Monitoring*
- Ultrasound Services*
- Same day reporting
- 24 Hour Service
- Seven days a week

*by appointment only



We service the entire Greater Rhode Island area:

- Nursing and Convalescent Homes
- Shut-ins and Private Home Patients
- Post Surgical Patients

PORTABLE X-RAY SERVICE

OF RHODE ISLAND

Certified by the R.I. Department of Health. Reimbursement provided by Medicare, R.I. Blue Shield and Medical Assistance.

100 Highland Avenue Providence, R.I. 331-3996	120 Dudley Street Providence, R.I 331-3996	154 Waterman Street Providence, R.I 273-0450	38 Hamlet Avenue Woonsocket, R.I. 766-4224

In The Beginning

Kimberly A. Poulton
Stanley M. Aronson, MD

The *Rhode Island Medical Journal* published its inaugural issue seventy five years ago. The lead editorial of this first issue appears below:

"The King is dead –long live the King." With the issue of November, 1916, the Providence Medical Journal, which has served the medical public of this state for seventeen years, went out of existence. With the New Year is born a new publication, THE RHODE ISLAND MEDICAL JOURNAL. New in name, it is still the old familiar friend which has come to our desks every two months these many years. The change in name and ownership was made in order that the JOURNAL might obtain additional financial support. The local field had been thoroughly canvassed and found to yield an insufficient revenue. Accordingly the JOURNAL was purchased from the Providence Medical Association and is now the property of the Rhode Island Medical Society. As the JOURNAL is now owned by the State Society, we are in a position to receive aid from the Co-operative Medical Advertising Bureau, under the auspices of the American Medical Association. By the terms of this agreement the JOURNAL must be published monthly, and all advertisements must be approved by the Council of the American Medical Association. We have conformed to the standard set by other state-owned journals and have increased the size of our page, used double instead of single column reading page, and have made our title page and contents uniform with the other state journals. The change in the JOURNAL has resulted in the loss of much advertising patronage. This will be compensated for by the addition of considerable other advertising obtained through our new affiliations. It is a source of satisfaction, in which every reader can share, that the advertising pages of the JOURNAL are as clean as that of any medical publication in the country. The Providence Medical Journal served the whole state, but never received the support it deserved from the district societies. Now that every member of the Rhode Island Medical Society feels a sense of proprietorship, we hope the district societies will give the JOURNAL the support it deserves and must have. We need cooperation. We wish all the medical interests of the entire state to collaborate in the production of a journal which shall represent the state as truly in reality as it does in name. As our literary miss makes her bow under her new name, we bespeak for her a hearty support, believing that her sphere of usefulness is to be greatly increased."

The editorship of the new statewide publication was assumed by Roland Hammond, MD, a 1902 Harvard Medical School graduate and a practicing orthopedic surgeon. He was later elected to the presidency of the Rhode Island Medical Society (1935-36) and died in 1957.

In the year 1917 the officers of the Rhode Island Medical Society convened only four times each year, on the first Thursday of the designated months. Annual membership dues were five dollars. The President of the Society in 1917 was Edmund D. Chesebro, MD, an 1887 graduate of Brown University who received his medical education at the Columbia College of Physicians and Surgeons. He practiced pediatrics in Providence for over six decades and organized and headed the Pediatrics Department at St. Joseph Hospital. Dr Chesebro died in Greenville, Rhode Island, in 1956.

Franklin

The Ideal Doctor's Car

Why haul around Two tons of freight to do your work? —it costs money; is dangerous and tires the nerves. The Franklin car will do your work 50 to 75% cheaper; is more comfortable than any other car in the World; will stand out in the cold indefinitely without freezing and start in ten seconds. If you have never had a demonstration, arrange one at once as you have a lot to learn about Motor Cars.

WALLACE L. WILCOX
635 Elmwood Avenue Telephone Broad 1816 1428

The many editorials of the 1917 Journal issues would seem eminently relevant in the Rhode Island medical atmosphere of the 1990s. These commentaries addressed such subjects as workmen's compensation legislation, improvements in medical education, the move from general practice to specialization, interstate reciprocity for physicians, the need to increase membership in the State Society, and of course, the call for medical preparedness as the war in Europe inevitably expanded. A handful of months before our active participation in World War I, the *Journal* noted:

"Before these words are in print it is possible that this nation may be involved in a stupendous crisis. If such a calamity should occur, we know that every physician will be anxious to devote his energies and talents to the service of his country. We are convinced that his personal feelings or his opinions regarding the virtues of pacifism or militarism will not stand in the way of patriotic duty. It is a source of satisfaction of the profession to know that the medical records of his country have been thoroughly investigated and the information placed at the disposal of the Surgeon General of the Army. In this work the State Committee of the Committee of American Physicians for Medical Preparedness had its share and has carefully tabulated the data for Rhode Island. We seriously urge every physician in the state to prepare for service to our country and to be ready for duty if the call comes."

A February, 1917 editorial is reprinted below since it voices so accurately, and eloquently the views of the current Publications Committee and Editorial Board:

"The Editorial Staff of THE RHODE ISLAND MEDICAL JOURNAL is desirous that the periodical shall accurately reflect medical opinion throughout the state. For this reason we wish to obtain an expression of opinion from as many physicians as possible in the state on some subject which seems to them of vital interest to the medical profession. Most physicians . . . may have acquired a philosophy in the practice of medicine which will be of benefit to some fellow practitioner. Medical legislation of vital interest to the future welfare of the profession will soon be enacted by our legislative bodies, and amendments to existing laws are urgently demanded. We hope the individual members of the profession will be willing to embody their ideas in the form of a letter to be published in the JOURNAL as space will permit. Communications dealing with matters of interest to the profession will find a place in these columns."

What was Rhode Island like in January of 1917? It was a thriving industrial state with a population of 895,986 people. Providence, in 1917, had slipped from being the 20th largest city in the United States to the 23rd position.

The state had recently reelected Governor N. Livingston Beeckman, Republican, for his second term. Providence's mayor was Joseph Gainer, a member of the Democratic party. The state's two Senators were: LeBaron Colt of Bristol (Republican) and Peter Gerry of Warwick (Democrat). Gerry's election in 1916 represented the first time that senators were chosen by direct popular ballot (Constitutional Amendment XVII, ratified on May 31, 1913). The state was represented by three congressmen, rather than the current two. During the 1916 presidential election, which was won by Mr. Woodrow Wilson, a Democrat, the state voted overwhelmingly for Mr. Charles Evans Hughes, a Republican and a graduate of Brown University. Who may vote in Rhode Island in the year 1917? "Every male citizen of the United States of the age of 21 years who has had his residence and home in this State for two years, and in this city six months, has been registered, . . . and who is really and truly possessed in his own right of real estate in this city of the value of $134 over and above all encumbrances. . ."

Salaries of state officials varied from $6,500 per annum (Chief Justice of the Supreme Court) to $500 (Sealer of Weights and Measures). The Governor was paid $3,000.

There were 96,490 children attending the public schools of Rhode Island. And supervising them were 2,680 teachers each earning an average annual salary of $714.37. The total yearly statewide budget for education was $2,903,068. Brown was a small Baptist University on College Hill. Its President was the Rev. William H.P. Faunce and its 1916-17 football team achieved eight victories in nine games, losing only to Colgate.

Providence's leading newspaper was the *Daily Journal*, established in 1829 and selling for two cents. The leading stories during the month of

KELLY-SPRINGFIELD TIRES

There are two ways of telling a good automobile tire One way is to put it on your car, but the better way is to look for the name Kelly Springfield on the side Let us serve you

BELCHER & LOOMIS HARDWARE CO.

83-91 Weybosset St. PROVIDENCE, R. I.

Prescribe

"Horlick's"

the Original and Genuine

Endorsed by the medical profession, who for over a third of a century have proven its reliability in the feeding of infants, nursing mothers, convalescents, and the aged.

Samples prepaid upon request

Horlick's Malted Milk Co.
Racine, Wisconsin

★ ★ ★ HERE

is one of the advertisements of The Sugar Institute

THE advertisement reproduced here is one of the series appearing in publications throughout the country. In order to keep the statements in accord with modern medical practice, they have been submitted to and approved by some of the leading authorities in the field of human nutrition in the United States. The Sugar Institute, 129 Front Street, New York.

SCHOOL CHILDREN'S

appetites **ARE**

fickle

...OFTEN DUE, HOWEVER, TO TASTELESS OR UNINVITING DIET

THOSE in charge of school luncheons are often confronted with the problem of getting children to eat what is good for them.

The lack of taste-appeal in the food served is often the reason that food is rejected or "picked at." Cooked tomatoes may be too tart, the stewed fruit insipid, the spinach and the carrots bland.

By flavoring or seasoning these essential foods with sugar they will be much improved in flavor. A dash of sugar to a pinch of salt is a good rule to follow in seasoning string beans, carrots, peas, tomatoes, soups and meat and vegetable stews. Fresh and cooked fruits should be sweetened to taste.

Doctors and diet authorities approve this use of sugar because it makes those foods which are carriers of vitamins, minerals and roughage, more enjoyable to the child. Flavor and season with sugar. The Sugar Institute, 129 Front Street, New York City.

"Flavor and season with Sugar"

January 1917 dealt mainly with the bloody though deadlocked conflict in Europe, called then the War of Nations. President Wilson was attempting to mediate between the warring nations despite " . . . the Luisitania crisis." Secretary of State Lansing was the active negotiator, but the peace initiatives gained little support except from King Constantine of Greece. The allied governments insisted that the German armies retreat from Belgian territory and pay reparations for damages. The Kaiser's reply, said the newspaper, ignored the demands for retreat and merely lauded the gallant work of his U-boats. Indeed, each day's newspaper carried further tragic stories of the numerous ships sunk by torpedoes. There were companion stories which talked darkly of possible German manipulation of the New York Stock market. In New Jersey, munitions dumps were set afire, creating what was then described as the largest explosion in human history. There was some suggestion of sabotage. The German Consul General was also accused of planning the explosion of munitions ships docked in west coast ports.

Yet another story which occupied the January 1917 news pages concerned a major leak of privileged information in Washington. The government brought suit against some legislators for leaking information to the press. The progress of Señor Villa's revolutionary army in Mexico was an almost daily news item, as was Mexican President E. Zapata's attempt to achieve a political compromise with the rebels. Other stories from Europe told of the plight of Belgian refugee children; terrible floods in the lowlands of Holland unprotected by dikes; and the gradual dissolution of the various provisional governments in Imperial Russia. Poles in exile were looking forward to an independent Polish kingdom; and meetings of Zionists in Providence expressed the hope that someday there would be a Jewish state in the middle east. In Washington, suffragettes were silently picketing the White House.

Local news stories included the arrest and trial of five Rhode Island physicians for illegal drug traffic. They were specifically accused of distributing morphine to addicts, contrary to the provisions of the Harrison Drug Act. There was increasing discussion of the prohibition of alcoholic beverages. On New Year's Eve, New York City required that revelry cease shortly after midnight, all taverns be closed by 1 AM and that no strong spirits be served after that hour. Congress declared that the District of Columbia was henceforth "dry" although there was nothing to prohibit the purchase of whisky in Maryland or Virginia.

Gainer, just elected mayor of Providence, outlined his political agenda: establish bacteriological standards of milk sold in Providence; create a public school commission; install a city-wide fire alarm box network; place electric conduit lines underground; have garbage collected by the city; establish speed limits for gasoline-driven vehicles on the city streets.

Most sports stories described boxing bouts and the activities of local ice hockey teams. The Red Sox, who had just won the American League championship, were seeking a new manager. In the local theaters, the leading play was "War Brides" starring the great Nazimova, prices ranging from 10 to 25 cents. Movie theaters were alternating films with live band concerts, although some houses advertised "continuous showings."

Deaths during the month of January, 1917 included the great Colonel William Cody (Buffalo Bill) and Admiral George Dewey. A small item mentioned the drowning in the river Neva of a Russian monk named Gregory Rasputin.

Economic news: Stock market prices included AT&T 1 7/8, Santa Fe 103 1/2; General Motors 121; Liggett & Myers 277 1/2 and US Steel 106 1/4. Local stories noted rapid rises in food prices. Anthracite coal, the principal source of home heat was selling

for an exorbitant $10.75 per ton. Pennsylvania crude oil could be obtained for $3.05 per barrel.

Principal advertisers in the Providence *Daily Journal* were Shepard's Department Store, Outlet Co. Gladdings, Tilden & Thurber, Edison Phonograph, and Cadillac, Franklin and Overland motor cars.

These seventy five years had surely produced major technical changes both in medicine and the everyday world around us; the human dimension of life, however, seemed to have changed only slightly. "Human history," observed H.G. Welles, "becomes more and more a race between education and catastrophe."

The advertisements included with this article are reprinted here from earlier issues of the *Rhode Island Medical Journal* to convey a sense of the era.

Always Specify BLANDING

LINOMUL

(BLANDING)

COMPOUND FLAXSEED EMULSION

PALATABLE AND PERMANENT

Indicated in Pulmonary Diseases, Chronic Coughs and Colds, Acute and Chronic Bronchitis, After Effects of Influenza, Wasting Diseases, Rickets, Scrofula, Whooping Cough and General Debility

DOSE
Adults Tablespoonful 3 or 4 times a day
Children 1 or 2 teaspoonfuls according to age

Prepared in the laboratories of
BLANDING & BLANDING
PROVIDENCE, R. I.

It is best to start with a small dose and gradually increase to the regular dose

JANUARY, 1952

when other external therapy seems to get **nowhere...**

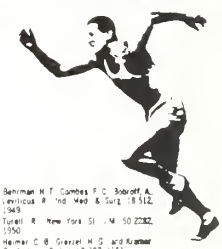
accelerate healing with

Study[1], after study[2] after study[3] corroborates the "notable"[1] success of Desitin Ointment in easing pain and stimulating smooth tissue repair in lacerated, denuded, chafed, irritated, ulcerated tissues—often in stubborn conditions where other therapy fails.

DESITIN OINTMENT
the pioneer external cod liver oil therapy

in **wounds** especially slow healing
burns
ulcers decubitus, varicose, diabetic

Protective, soothing, healing. Desitin Ointment is a non-irritating blend of high grade crude Norwegian cod liver oil (with its unsaturated fatty acids and high potency vitamins A and D in proper ratio for maximum efficacy), zinc oxide, talcum, petrolatum, and lanolin. Does not liquefy at body temperature and is not decomposed or washed away by secretions, exudate, urine or excrements. Dressings easily applied and painlessly removed. Tubes of 1 oz., 2 oz., 4 oz., and 1 lb. jars.



write for **samples** and literature

DESITIN CHEMICAL COMPANY
70 Ship Street, Providence 2, R. I.

1. Behrman, H. T., Combes, F. C., Bobroff, A., Leviticus, R.: Ind. Med. & Surg. 18:512, 1949.
2. Torell, R.: New York St. J. M. 50:2282, 1950.
3. Heimer, C. B., Gravel, H. J., and Kramer, B.: Archives Pediat. 68:382, 1951.

STOWELL B. SHERMAN

E. E. BERKANDER

Sherman-Berkander Co.

Manufacturing Opticians

Oculists' Prescription Work Our Specialty

"Accuracy"
"Courtesy"
and
"Service"

Discount
to Physicians and Nurses

268 Westminster Street Providence, R. I.
(Opposite Shepard's Clock)

PHYSICIAN OFFICE SUPPLY COMPANY
ESCO DRUG CO., INC.

110 Lockwood Street
Providence, Rhode Island

Mark S. Goldberg, R.Ph., B.S., M.B.A.
Pharmacy Manager
421-3250
FAX 621-9889

- vaccines
- injectables
- chemotherapeutics
- paper products
- surgical dressings
- specialty compounding: progesterone suppositories
- trained orthotic fitter
- Jobst, Vairox, Warm and Forms
- RI Leading Diabetic Supplier

*** BEST PRICES AROUND ***

CALL FOR A PRICE QUOTE

STORE HOURS
Monday thru Friday 8:00 AM to 6:00 PM
Saturday 9:00 AM to 1:00 PM

Featuring Schering's Intron A (Interferon alfa 2b), Eulexin (Flutamide), Proventil Family (albuterol).

YOUR TREES DESERVE
THE BEST OF CARE
Trees are valuable assets.
Don't entrust their future to less
than caring professionals.
Bartlett leads the way in tree care
with trained arborists, research facilities,
nationwide experience and specialized
equipment. For a professional evaluation
of your tree care needs, call today.
There is no obligation.

All Phases of Tree Care: Residential and Commercial

LOCAL OFFICES.
Seekonk, MA
508-336-9330
North Kingston, RI
401-884-2885

Scientific tree care since 1907
BARTLETT TREE EXPERTS
Corporate Office STAMFORD, CT

Backed by the Bartlett Research Laboratories and Experimental Grounds
Charlotte, North Carolina

©1991 Bartlett Tree Experts

PHYSICIAN IMMEDIATELY

BC/BE
FAMILY PRACTICE/INTERNAL MEDICINE

Successful family practice group is seeking an additional physician for a satellite office. Basic guaranteed salary plus incentives and fringe benefits. An excellent, lucrative opportunity for an aggressive physician at no start-up costs.

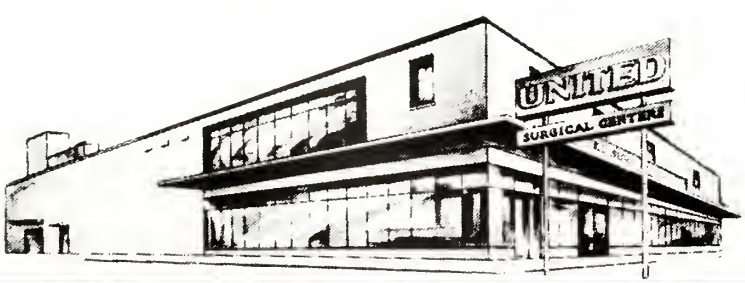
Reply to

BOX P
RHODE ISLAND MEDICINE
106 Francis Street
Providence, RI 02903

There must be a good reason why we've become the trusted back-up resource for more Rhode Island doctors (and their patients) than anyone else.

UNITED SURGICAL CENTERS

The Professionals in Home Health Care Equipment



We carry just about EVERYTHING for Home Health Care . . . which means, everything a patient or convalescent needs to implement the doctor's treatment directions. For Ostomy and Oxygen needs to Orthopedic Appliances, Wheelchairs, Walkers and Hospital Beds, we're here to serve your patients. Our staff is knowledgeable and dedicated to supplying exactly "what the doctor ordered". We've been doing it dependably for many years.

That's how we've earned the trust of so many doctors.

Medicare and Third Party Claims Accepted and Processed.

380 WARWICK AVE., WARWICK
781-2166

THE RHODE ISLAND MEDICAL JOURNAL

The Official Organ of the Rhode Island Medical Society
Issued Monthly under the direction of the Publication Committee

VOLUME I
NUMBER 1

PROVIDENCE, R. I., JANUARY, 1917

PER YEAR $2.00
SINGLE COPY, 25 CENTS

THE RHODE ISLAND MEDICAL JOURNAL HERITAGE

Ninety Years Ago
(Providence Medical Journal)
(January, 1902)

An editorial, entitled The New Medical Act, endorses recent legislature passed by the state of Rhode Island providing greater authority to the State Board of Health in allowing more rigid investigation of the diplomas of applicants seeking medical licensure in the state. It also allows for the professional testing of new applicants. It is hoped, declares the editorial, that "This measure . . . will keep out incompetent and undesirable practitioners." The new law may also be a step towards reciprocity between various state licensing boards.

A second editorial notes that a Legislative Committee to study the feasibility of establishing a Rhode Island sanatorium for tuberculosis has now reported favorably. A bill has now been introduced, notes the editorial, ". . . providing for the appointment of a commission, and the appropriation of $100,000 for the purchase of land, and erection of the necessary buildings."

A third editorial called, An Imported Weakness, expresses profound concerns not only about anarchists immigrating to the United States, but also "the hundreds of weak minded semi-dements and degenerates." The editorial notes, "There are few hospital (for the insane) records that will show less than 40% of the inmates to be foreign born. . . " The editorial concludes: "It is time that the lawmaking power realized these facts and more securely guarded our country, not only from the anarchist, but from others "conspicuously unfit – the weak-minded, degenerate, and insane."

The first of the original communications to the Journal, written by Walter L. Munro, MD, is an article on epidermoid carcinoma, with some reference to its fraudulent treatment by cancer quacks. The article describes quack therapies such as caustic pastes for breast cancer and herbal concoctions for cancers of the oral cavity. And yet, the author observes, many of these quacks are financially quite successful. He tells a story of a conversation with one of the most successful. "You'll admit, you don't know much about medicine; how do you account for the fact that your office is constantly full of people, while I am doing only a living business?" The quack replied: "Come to the window a minute. Do you see that group of men, seven of them aren't there? Well how many of those men do you suppose to be gifted with sound common sense?" "Possibly one," said Dr. X. "All right," said the quack, "you may have him for a patient; I'll take the other six." (Ed. note: This article is unusual, for 1902, in that there are numerous clinical photographs illustrating the neoplastic lesions of the oral cavity.)

George F. Keene, MD writes on some phases of epilepsy and the epileptic constitution. "The pathology of epilepsy," says the author, "is as yet almost a sealed book. The most we can say is that it is probably of central or cerebral origin. He goes on to observe: "We know, also, that upon the epileptic state or constitution are sometimes engrafted very similar manifestations, which have been classed under the head of automatism or secondary automatic states." He then illustrates his contention with specific case reports showing the undertaking of criminal actions, including motiveless murder, while under the influence of seizures.

Seventy-Five Years Ago
(January, 1917)

No longer the Providence Medical Journal, this is the inaugural issue of the Rhode Island Medical Journal.

The first of the original articles is by Frank Peckham, MD describing lateral curvature of the spine (scoliosis) and an original method of nonsurgical treatment. After reviewing the various etiologic agents which may possibly cause scoliosis, the author describes

his newer therapy consisting of plaster jackets surrounding the thorax and the use of a convex frame to reduce gradually the deformity.

The second article by Harry Bernstein, MD outlines the experiences within the office of State Pathologist. Principal tests included (in order of volume) diphtheria cultures, sputa for tuberculosis, bacteriological examination of water, Widal reactions, smears for gonococcus, surgical specimens, smears for malaria, and post-mortem examinations.

The third article, by William Harris, MD, describes the anatomic variation called the pelvic appendix, with means to facilitate its clinical recognition when inflamed.

Two brief comments are included: One listing the preventive virtues of a yearly medical examination, especially in individuals older than age 30. The second endorses a campaign against wood alcohol which is sometimes incorporated in bay rum and other toilet articles, shellac, and soft drinks.

Fifty Years Ago
(January, 1942)

George Alexander, MD writes an article on therapeutic psychoanalysis, noting that it is but fifty years since a new theory on the origin and structure of neurosis was proposed to the medical profession. He concludes, "Despite the handicaps imposed upon therapeutic psychoanalysis from within and from without, it has however continued to make valuable contributions to the understanding and treatment of illness for almost fifty years. Its theories and techniques in modified forms are so deeply imbedded in modern medicine that they cannot avoid participating in the future growth of medical art and science. Psychoanalysis has survived its own infancy and has passed through most of its childhood conflicts. Insofar as one may glimpse its future, it now seems assured of reaching a full maturity and the capacity to live in increasing harmony within the environment of medicine."

Walter Jones, MD summarizes 273 cases of toxemia of pregnancy derived from the records of Providence Lying-In Hospital. In Group B, 26.4% were mildly preeclamptic, 20.6% severely preeclamptic and 5.9% eclamptic. The author concludes: "In the past three and a half years, the Toxemia Clinic has seen 273 cases. Mild hypertension, mild preeclampsia and severe preeclampsia are discussed."

The lead editorial begins with the following paragraph: "The nation is at war. The Congress has passed an amendment to the Selective Service act which will call for registration of every man up to the age of 65 and which will place all men under 45 years of age subject to service at the order of the Selective Service boards."

The Journal also notes that the Rhode Island Council of Defense has organized appointments of City and Town Directors of Medical Aid for each of the incorporated urban regions of the state.

Twenty-Five Years Ago
(January, 1967)

The lead article entitled Clinical and Experimental Experiences with Cuffed Tracheostomy Tubes, by Francis McNelis, MD first discusses the recent development of intermittent positive pressure breathing to assist or control respiration through artificial means. The author discusses his experiences in 116 tracheostomies performed during 1964, 40 of which employed a cuffed tracheostomy tube. He concludes: "I feel intermittent positive pressure breathing can be administered without tracheal complications when the basic fundamentals of proper tracheostomy and after-care are observed. The best results are obtained with the largest tube that can be accommodated. The use of an oral or intranasal tube is to be condemned, except as an emergency measure until the proper tracheostomy can be performed."

Mario Tami, MD provides a paper on acute fulminating moniliasis. He notes that this organism had often been considered a harmless saprophyte, perhaps responsible at most for localized superficial infections (thrush). Beginning in the second half of this century there were increasing numbers of published reports describing fulminating and disseminated infections with Candida genus organisms.

The author summarizes: "A case of monilial infection is presented, characterized by a fulminating course, leading to death 42 hours after admission to the hospital. The patient was a fifty-year-old white woman, a mild diabetic, who had been given a short course of antibiotic treatment three weeks prior to admission. The clinical picture was that of postprandial abdominal pain in the three weeks prior to admission then excruciating abdominal pain on admission, followed by coma, shock and death. A chest X-ray study on admission was entirely unremarkable, while post mortem examination 42 hours later disclosed acute, diffuse monilial pneumonia. A 20 cm segment of proximal ileum showed evidence of purplish discoloration and a microscopic picture of diffuse necrotic hemorrhagic enteritis with infiltration of monilia within the tissue."

Tadeusz Rozycki, MD offers an epidemiological and clinical analysis of measles encephalitis in the state of Rhode Island. He compares the results of the most recent 15 year interval (1953 to 1966) with a prior 15 year survey conducted in the same hospital (the Charles V. Chapin Hospital of Providence). During the 1937-1952 interval there were 35 cases of measles encephalitis amongst 51,031 cases of measles (incidence rate = 0.7/1,000 cases of measles) and a mortality rate of 20%. During the 1953-1966 interval there were 50 cases of measles encephalitis amongst 34,800 cases of measles (incidence rate=1.4/1,000 cases of measles) and a mortality rate of 4%. The author notes that the highest incidence was found in the early school age group and especially in females. Late sequelae (epilepsy, paresis, personality changes, emotional instability, loss of intelligence and chronic headache) were found in 52% of the patients treated symptomatically, but in only 20% of those on steroids. No side effects of steroids were observed.

PSYCHIATRIST

Brown University Dept. of Psychiatry
Affiliated Program

Currently recruiting for Medical Director of Partial Hospitalization Program. For this exciting new program, the position requires a Board Eligible or Board Certified Psychiatrist for 20 hours per week, Massachusetts License required. Health benefits and a Brown appointment are possibilities for the right candidate. Interested applicants please contact:

James Reich, MD
Associate Medical Director
Corrigan Mental Health Center
49 Hillside Street
Fall River, MA 02720

(508) 670-2901
Monday through Friday, 9 am to 5 pm

1000 SQ. FT.

Recently completely renovated
1st floor

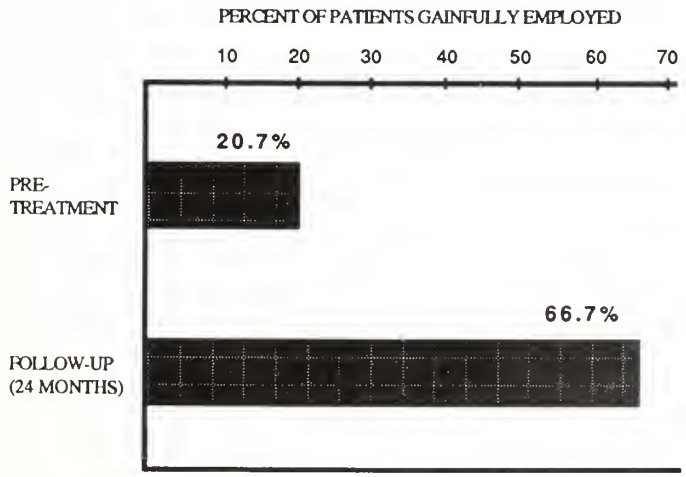
Large office space includes
3 examining rooms, consultation
room, reception area.

AVAILABLE NOW

Medical Building
1524 Atwood Avenue
Johnston

CALL 521-6080

"CHRONIC PAIN DOESN'T HAVE TO MEAN
CHRONIC DISABILITY FOR YOUR PATIENTS..."

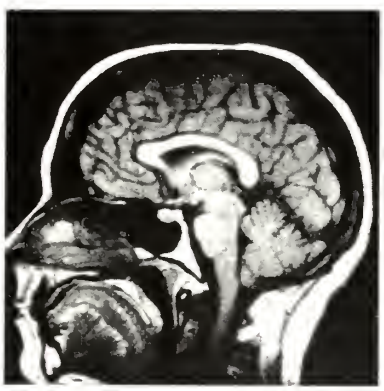


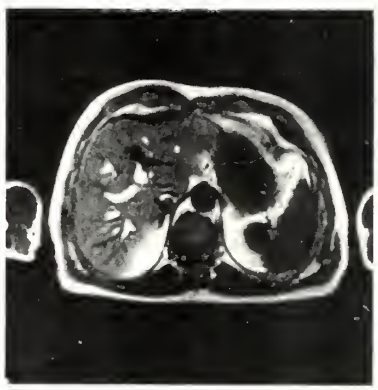
The Chronic Pain Treatment Program
(401) 751-9150

Institute for Behavioral Medicine
120 Wayland Avenue
Providence, Rhode Island 02906-4318

RI-MASS MRI, P.C. is pleased to sponsor the

2ND WEDNESDAY LECTURE SERIES





WHEN: The 2nd Wednesday
of each month
6:30 p.m. - 7:30 p.m.

WHERE: Marriott Hotel
Charles at Orms
Providence, RI 02904

THIS MONTH'S TOPIC:
"Spinal Tumors: Current Status and Recent Advances"
Wednesday, January 8, 1992

NEXT MONTH'S TOPIC:
"Knee and Wrist MRI: Current Experience"
Wednesday, February 12, 1992

TO REGISTER/CALL: 1 (800) 848-9661

Rhode Island

MD
NEEDED

for private walk-in primary care facility. Up-to-date equipment. Full staff of professionals.

Must be experienced in minor surgery and orthopedics.

30-40 hours per week. Malpractice insurance. Vacation. Position available early 1992.

Please send resume to:

Box M
RHODE ISLAND MEDICINE
106 Francis Street
Providence, RI 02903

Need Information about Businesses? Call the Business *INFOLINE!*

There are over 9 million businesses in the U.S. – and finding information about them can be virtually impossible, especially when you need it *fast*. But now there's a way . . . a revolutionary new service called *Business INFOLINE!* Need to know the address and phone number for "XYZ Company" somewhere in Florida, or the name and phone number of a "Cadillac Dealer" in Palm Beach? Even telephone company directory assistance can't help you in these situations . . . but we can!

For example . . .

"Your BMW breaks down on the interstate, and you need to know if there 's a dealer in the next town."

"An out-of-town company is trying to sell you vinyl siding for your house and you need more information about them – how long the company has been in business, and how many employees they have."

"You're planning a vacation in the Pacific Northwest, and you want to line up things for the kids to do. So you need to find the amusement parks and zoos in Oregon and Washington."

"A friend gave you a tip that "Apex Industries" would be a good investment, but you want to know more. What do they do? What are their approximate annual sales?"

The Business INFOLINE is indispensable for home or office? And the cost is *only* $3.00 for the first minute and $1.50 for each additional minute, conveniently billed to your phone number. The service is available Monday through Friday, 7:00 a.m. to 6:00 p.m., Central Time.

Dial 1-900-896-0000

Ask for Ext. #195

Money-back Guarantee if not satisfied.

A Service of American Business Information • 5711 So. 86th Circle • Omaha, NE 68127

RUN A SPECIAL PRACTICE.

Today's Air Force has special opportunities for qualified physicians and physician specialists. To pursue medical excellence without the overhead of a private practice, talk to an Air Force medical program manager about the quality lifestyle, quality benefits and 30 days of vacation with pay each year that are part of a medical career with the Air Force. Discover how special an Air Force practice can be. Call **USAF HEALTH PROFESSIONS TOLL FREE 1-800-USAF**

AIR FORCE

NECROLOGY 1991

Joseph P. Nourie, MD

Doctor Joseph P. Nourie, a Providence physician for 50 years before retiring in 1977, died April 1, 1991, at the age of 90.

Doctor Nourie graduated from Tufts University Medical School and interned at Rhode Island Hospital in 1923. For many years he was a medical examiner in North Providence. He was on the staff of the former Our Lady of Fatima Hospital, St. Joseph and Roger Williams General Hospital. Doctor Nourie was a member of the Rhode Island Medical Society, the New England Medical Society, and the American Medical Association.

William J. MacDonald, Sr., MD

Doctor William J. MacDonald, Sr., former chief of obstetrics at Women & Infants Hospital, died May 1, 1991 at the age of 72.

In 1943, Doctor MacDonald graduated from Cornell Medical College and served his internship at Rhode Island Hospital. In 1944, he was one of the first three residents in obstetrics and gynecology at the former Lying-In Hospital, now Women & Infants. He also served a residency in gynecology at Women's Hospital of New York.

Doctor MacDonald was instrumental in the planning for the Brown University Medical School in the early 1970s when he was president of the Rhode Island Medical Society. He later became professor-emeritus in obstetrics and gynecology at the medical school. Doctor MacDonald was chairman of the board of directors of the Rhode Island Blue Shield from 1976 to 1982, and was vice chairman of Blue Cross & Blue Shield of America. In 1970, he was appointed to the Governor's Commission on Health Care Cases.

Doctor MacDonald was vocal on a number of issues involving the state's medical community throughout the 1960s and 1970s. He urged the General Assembly to pass a law protecting the life of the fetus, arguing that a fetus is a human being. He also called for consolidation of all obstetric care in the greater Providence area at Women & Infants Hospital.

Past president and treasurer of the Providence Medical Association, Doctor MacDonald was also the former chairman of the Rhode Island Chapter of the American College of Obstetrics & Gynecology, a member of the American Medical Association, the New England Obstetrics & Gynecology Society, and the Obstetrical Society of Boston.

Doctor MacDonald was the husband of Estelle (Gregory) MacDonald.

H. Frederick Stephens, MD

Doctor H. Frederick Stephens, an ophthalmologist in private practice until 1985, died June 13, 1991, at the age of 81.

Doctor Stephens graduated cum laude from the Medical College of Syracuse in 1934. He interned at Syracuse Memorial Hospital and Rhode Island Hospital. Completing his residency at Massachusetts Eye and Ear Infirmary in April 1939, Doctor Stephens was certified by the American Board of Ophthalmology in 1940.

He was a Navy commander during World War II and served as a flight surgeon with the First Marine Aircraft Wing in the South Pacific. Doctor Stephens was honored with a special award for service by the Rhode Island Society for the Prevention of Blindness, by USAID for service in Laos and Care-Medico Award for service in Algeria.

Doctor Stephens was Surgeon-in-Chief, Department of Ophthalmology at Rhode Island Hospital from 1949 to 1974. He founded the Residency Training Program in ophthalmology in 1965 and served as its director until 1974. He also served as Chief of Staff of the hospital in 1960. Doctor Stephens was a consulting surgeon in Ophthalmology for several hospitals in the region.

Doctor Stephens held membership in the Rhode Island Medical Society, Providence Medical Association, American Medical Association, Association for Research in Ophthalmology, American Academy of Ophthalmology, Pan American Association of Ophthalmology, American Association of Ophthalmology, Society of Eye Surgeons, International Eye Foundation, Medico, and New England Ophthalmological Society, of which he was a past president. Because of his volunteer medical service through the years, he was inducted as a 33rd degree Mason.

Doctor Stephens was the husband of Mary (Van Benschoten) Stephens..

Casimir J. Miga, MD

Doctor Casimir J. Miga, Deputy Medical Director at Zambarano Memorial Hospital before retiring in 1969, died July 24, 1991 at the age of 85.

A graduate of Georgetown University Medical School, Doctor Miga interned at St. Joseph and Charles V. Chapin Hospitals. He began private practice in 1932 and was on the staff of St. Joseph, Roger Williams and Chapin Hospitals. He joined Zambarano Hospital in 1941, where he was appointed assistant superintendent in 1950.

Doctor Miga was a member of the Rhode Island Medical Society, the Providence Medical Association, and the American Thoracic Society.

Doctor Miga was the husband of Hope C. (Searles) Miga.

Edward H. Trainor, MD

Doctor Edward H. Trainor, a practicing physician and surgeon with an office at Summit and Walcott Streets for more than 50 years before retiring in 1974, died August 21, 1991, at the age of 87.

Doctor Trainor graduated from Georgetown University Medical School and was on the staff of Memorial Hospital, Notre Dame Hospital, and St. Joseph Hospital.

INFORMATION FOR AUTHORS

Manuscripts: Manuscripts will be accepted for consideration with the understanding that they are original contributions, have never been published or submitted elsewhere, and are submitted only to the *Rhode Island Medical Journal.*

Specifications: Manuscripts must be original typed copy (not all capitals) on 8½ × 11 inch firm typewritten paper, double-spaced throughout (including title page, text, acknowledgments, and references) with margins of at least one inch and using but one side of each page. Tables, charts, and legends should be submitted separately from the text, and referred to by number (ie, Fig. 1) within the text. Subheadings must be inserted at reasonable intervals to break the typographic monotony of the text. Pages must be numbered consecutively. Italics and boldface print are never used except as subheadings.

Abbreviations: The *Journal* attempts to avoid the use of jargon and abbreviations. All abbreviations, especially of laboratory and diagnostic procedures, must be identified in the text.

Title Page: All manuscripts must include a title page which provides the following information: (1) a concise and informative title; (2) the name of the author or authors with their highest academic degree (ie, MD, PhD); (3) a concise biographical description for each author which includes specialty, practice location, academic appointment, and primary hospital affiliation; (4) mailing address and office telephone of principal author; (5) mailing address of author responsible for correspondence or reprint requests; (6) source of support if applicable.

Illustrations: Authors are urged to use the services of professional illustrators and photographers. Drawings and charts should always be done in black ink on white paper. Clear, black and white 5 × 7 glossy photographs should be submitted, and such illustrations numbered consecutively and their positions indicated in the text. Original magnifications should be noted. Illustrations defaced by handwriting or excessive handling will not be accepted. The figure number, indication of the top, and the name of the author must be attached to the back of each illustration. Legends for illustrations should be typewritten on a single list, with the numbers corresponding to those on photographs and drawings. Recognizable photographs of patients are to be appropriately masked and must carry with them written permission for publication. Special arrangements must be made with the editors for excessive numbers of illustrations. Color plates are not acceptable.

Identification of Patients: Names, initials should not be used. Use of numbers is a preferable form of identification.

Reprints: Because of cost considerations, reprints are not provided routinely to the author(s). Reprints may be ordered separately (100 copies minimum order) and printing costs will be charged to the author(s).

Responsibility: Manuscripts are subject to editorial revisions as deemed necessary by the editors and such modifications will be undertaken so as to bring them into conformity with *Journal* style, which is in compliance with the editorial standards of the AMA. However, neither the editors, nor the publishers, nor the Rhode Island Medical Society will accept responsibility for statements made or opinions expressed by any contributor in any article or feature published in the pages of the *Journal.*

Permission: When material is reproduced from other sources, full credit must be given both to the author and publisher of these sources. Where work is reported from a governmental service or institution, clearance by the appropriate authority must accompany the manuscript.

References: To conserve space and expense, references should be limited to those essential to the subject. The editor reserves the right to reduce the number when it is deemed necessary. The references must be double-spaced and numbered as they appear consecutively in the text, with their positions clearly indicated in the text. All references must be checked to assure complete accuracy. Each journal reference must include the full name of the author(s); complete title of paper; name of publication; volume number; issue number; first and last page of paper; and date (year, month, and day as indicated). Each book reference must include the full name of author(s), editor(s), or both, with initials; title of book; edition; publisher; location; year of publication, volume (if given); and page number. If the reference is to a chapter within a book, the author of the chapter, if different than the author of the book, and the title of the chapter (if any) must be provided.

Correspondence: All correspondence relating to publication should be addressed to: Managing Editor, *Rhode Island Medical Journal*, 106 Francis Street, Providence, RI 02903.

ONCE DAILY 180mg Calan SR verapamil HCl 180 mg SUSTAINED-RELEASE CAPLETS

The recommended starting dose for Calan SR is 180 mg once daily. Dose titration will be required in some patients to achieve blood pressure control.

A lower initial starting dosage of 120 mg/day may be warranted in some patients (eg, the elderly, patients of small stature)

Constipation, which is easily managed in most patients, is the most commonly reported side effect of Calan SR

BRIEF SUMMARY

Contraindications: Severe LV dysfunction (see *Warnings*), hypotension (systolic pressure < 90 mm Hg) or cardiogenic shock, sick sinus syndrome (if no pacemaker is present), 2nd- or 3rd-degree AV block (if no pacemaker is present), atrial flutter/fibrillation with an accessory bypass tract (eg, WPW or LGL syndromes), hypersensitivity to verapamil.

Warnings: Verapamil should be avoided in patients with severe LV dysfunction (eg, ejection fraction < 30%) or moderate to severe symptoms of cardiac failure and in patients with any degree of ventricular dysfunction if they are receiving a beta-blocker. Control milder heart failure with optimum digitalization and/or diuretics before Calan SR is used. Verapamil may occasionally produce hypotension. Elevations of liver enzymes have been reported. Several cases have been demonstrated to be produced by verapamil. Periodic monitoring of liver function in patients on verapamil is prudent. Some patients with paroxysmal and/or chronic atrial flutter/fibrillation and an accessory AV pathway (eg, WPW or LGL syndromes) have developed an increased antegrade conduction across the accessory pathway bypassing the AV node, producing a very rapid ventricular response or ventricular fibrillation after receiving I.V. verapamil (or digitalis). Because of this risk, oral verapamil is contraindicated in such patients. AV block may occur (2nd- and 3rd-degree, 0.8%). Development of marked 1st-degree block or progression to 2nd- or 3rd-degree block requires reduction in dosage or, rarely, discontinuation and institution of appropriate therapy. Sinus bradycardia, 2nd-degree AV block, sinus arrest, pulmonary edema and/or severe hypotension were seen in some critically ill patients with hypertrophic cardiomyopathy who were treated with verapamil.

Precautions: Verapamil should be given cautiously to patients with impaired hepatic function (in severe dysfunction use about 30% of the normal dose) or impaired renal function, and patients should be monitored for abnormal prolongation of the PR interval or other signs of overdosage. Verapamil may decrease neuromuscular transmission in patients with Duchenne's muscular dystrophy and may prolong recovery from the neuromuscular blocking agent vecuronium. It may be necessary to decrease verapamil dosage in patients with attenuated neuromuscular transmission. Combined therapy with beta-adrenergic blockers and verapamil may result in additive negative effects on heart rate, atrioventricular conduction and/or cardiac contractility, there have been reports of excessive bradycardia and AV block, including complete heart block. The risks of such combined therapy may outweigh the benefits. The combination should be used only with caution and close monitoring. Decreased metoprolol and propranolol clearance may occur when either drug is administered concomitantly with verapamil. A variable effect has been seen with combined use of atenolol. Chronic verapamil treatment can increase serum digoxin levels by 50% to 75% during the first week of therapy, which can result in digitalis toxicity. In patients with hepatic cirrhosis, verapamil may reduce total body clearance and extrarenal clearance of digitoxin. The digoxin dose should be reduced when verapamil is given, and the patient carefully monitored. Verapamil will usually have an additive effect in patients receiving blood-pressure-lowering agents. Disopyramide should not be given within 48 hours before or 24 hours after verapamil administration. Concomitant use of flecainide and verapamil may have additive effects on myocardial contractility, AV conduction, and repolarization. Combined verapamil and quinidine therapy in patients with hypertrophic cardiomyopathy should be avoided, since significant hypotension may result. Concomitant use of lithium and verapamil may result in a lowering of serum lithium levels or increased sensitivity to lithium. Patients receiving both drugs must be monitored carefully. Verapamil may increase carbamazepine concentrations during combined use. Rifampin may reduce verapamil bioavailability. Phenobarbital may increase verapamil clearance. Verapamil may increase serum levels of cyclosporin. Verapamil may inhibit the clearance and increase the plasma levels of theophylline. Concomitant use of inhalation anesthetics and calcium antagonists needs careful titration to avoid excessive cardiovascular depression. Verapamil may potentiate the activity of neuromuscular blocking agents (curare-like and depolarizing); dosage reduction may be required. There was no evidence of a carcinogenic potential of verapamil administered to rats for 2 years. A study in rats did not suggest a tumorigenic potential, and verapamil was not mutagenic in the Ames test. Pregnancy Category C. There are no adequate and well-controlled studies in pregnant women. This drug should be used during pregnancy, labor, and delivery only if clearly needed. Verapamil is excreted in breast milk, therefore, nursing should be discontinued during verapamil use.

Adverse Reactions: Constipation (7.3%), dizziness (3.3%), nausea (2.7%), hypotension (2.5%), headache (2.2%), edema (1.9%), CHF, pulmonary edema (1.8%), fatigue (1.7%), dyspnea (1.4%), bradycardia HR < 50/min (1.4%), AV block total 1°, 2°, 3° (1.2%), 2° and 3° (0.8%), rash (1.2%), flushing (0.6%), elevated liver enzymes, reversible non-obstructive paralytic ileus. The following reactions, reported in 1.0% or less of patients, occurred under conditions where a causal relationship is uncertain: angina pectoris, atrioventricular dissociation, chest pain, claudication, myocardial infarction, palpitations, purpura (vasculitis), syncope, diarrhea, dry mouth, gastrointestinal distress, gingival hyperplasia, ecchymosis or bruising, cerebrovascular accident, confusion, equilibrium disorders, insomnia, muscle cramps, paresthesia, psychotic symptoms, shakiness, somnolence, arthralgia and rash, exanthema, hair loss, hyperkeratosis, macules, sweating, urticaria, Stevens-Johnson syndrome, erythema multiforme, blurred vision, gynecomastia, galactorrhea/hyperprolactinemia, increased urination, spotty menstruation, impotence.

4/11/91 • P91CA6277V

Address medical inquiries to
G.D. Searle & Co.
Medical & Scientific
Information Department
4901 Searle Parkway
Skokie, IL 60077

SEARLE G.D. Searle & Co.
Box 5110 Chicago, IL 60680

A91CA6148T

ONCE DAILY 180mg Calan SR verapamil HCl 180 mg
SUSTAINED-RELEASE CAPLETS
A MILD START IN MILD HYPERTENSION
When diet and exercise alone are not enough...
© 1991, G.D. Searle & Co.

FRANCIS A COUNTWAY LIB OF MED
EXCHANGE OFFICE
10 SHATTUCK STREET
BOSTON MA 02115

RHODE ISLAND MEDICINE

February 1992

Volume 75, Number 2

The Future of Anesthesiology

...A COUNTY LIB OF MED
...ANCE OFFICE
...16 SHATTUCK STREET
...BOSTON MA 02115

Are your investments as successful as you are?

If your hard work and success have allowed you to build a portfolio of $250,000 or more, we'd like to work with you.

account administrator who will act as your personal financial advisor and you'll be backed by a team of investment managers with a history of proven investment success.

{ Professionally Managed Investments }

Because at Citizens Bank, our Trust and Investment Management team can provide you with the exceptional service, experience, and performance that will help you get the most from your investments. You'll have an

To put us to work for you call Malcolm Starr at 456-7445. Because there's never been a better time for Citizens.

Trust and Investment Management Services

CITIZENS BANK

Citizens Trust Company/Citizens Savings Bank

RHODE ISLAND MEDICINE

EDITORIAL STAFF

Stanley M. Aronson, MD
Editor-in-Chief

Kimberly A. Poulton
Managing Editor

Hugo Taussig, MD
Book Review Editor

Seebert J. Goldowsky, MD
Editor-in-Chief Emeritus

EDITORIAL BOARD

*Edward R. Feller, MD
Chairman

*Joseph Amaral, MD

*Stanley M. Aronson, MD

Edward M. Belser, PhD, JD

Paul Calabresi, MD

*Richard A. Carleton, MD

Margaret Cololan, MSJ

*James P. Crowley, MD

*Peter A. Hollmann, MD

*Margaret A. Neill, MD

*Frank J. Schaberg, Jr., MD

*Fred J. Schiffman, MD

William J. Waters, Jr., PhD

*Member of Publications Committee

OFFICERS

Kathleen C. Hittner, MD
President

Robert E. Baute, MD
President-Elect

A. Robert Buonanno, MD
Secretary

Frances P. Conklin, MD
Treasurer

Richard Wong, MD
Immediate Past President

DISTRICT AND COUNTY PRESIDENTS

Fred Vohr, MD
Bristol County Medical Society

Joseph Salvatore, MD
Kent County Medical Society

Orest Zaklynsky, MD
Newport County Medical Society

David P. Carter, MD
Pawtucket Medical Association

James P. Crowley, MD
Providence Medical Association

Joseph R. Dotolo, MD
Washington County Medical Society

Patrick R. Levesque, MD
Woonsocket District Medical Society

Volume 75, Number 2 February 1992

TABLE OF CONTENTS

COMMENTARIES

63 Modern Day Practice of Anesthesiology
Kathleen C. Hittner, MD

This Priceless Gift to Humanity

A Dramatis Personae for the World of Anesthesiology

The Language of Epidemiology (VIII). Cumulative Incidence

CONTRIBUTIONS *Guest Editor–Kathleen C. Hittner, MD*
The Future of Anesthesiology

69 **Pain Management: Trends in the 1990s**
Gregory Towne, MD

75 **Ambulatory Surgery: The Anesthesiologist as a Leader**
John K. Hairabet, MD

81 **What Every Pediatrician Should Know about Pediatric Anesthesia**
Richard Browning, MD
Andrew Triebwasser, MD
Alan J. Weissburg, MD

90 **Preoperative Medical Evaluation: Minimizing Perioperative Risk**
Fred Rotenberg, MD
Carl Schwartz, MD

97 **Perioperative Right Ventricular Failure**
Arthur A. Bert, MD

105 **Specialty Medical Education in Anesthesiology**
Ronald L. Fischer, MD, FCCP

COLUMNS

112 **HEALTH BY NUMBERS**
Health Insurance Coverage in Rhode Island, 1990-1991

115 **THE RHODE ISLAND MEDICAL JOURNAL HERITAGE**

Cover: A print depicting an early anesthesiological procedure, from MEN: A Pictorial Archive from Nineteenth Century Sources, Dover Publications, Inc., New York.

Rhode Island Medicine is owned and published monthly by the Rhode Island Medical Society, 106 Francis Street, Providence, Rhode Island 02903, Ph: 401-331-3207. Single copies $2.00 — Subscriptions $20.00 per year (members of the Rhode Island Medical Society — $5.00 annually). Published articles represent opinions of the authors and do not necessarily reflect the official policy of the Rhode Island Medical Society unless clearly specified. Advertisements do not imply sponsorship or endorsement by the Rhode Island Medical Society. Second class postage paid at Providence, Rhode Island. ISSN 0363-7913 POSTMASTER: Send address changes to RHODE ISLAND MEDICINE, 106 Francis Street, Providence, RI 02903. National Advertising Bureau: State Medical Journal Advertising Bureau, Inc., 711 South Blvd., Oak Park, Illinois 60302. Phone 708-383-8800.

RIMS
Insurance Brokerage Corporation

Insurance Professionals serving Health Care Professionals.

We do it better!

- Because our purpose is to serve RI doctors and allied health care professionals.
- Because our staff has 15 years of solid experience in medical liability underwriting.
- Because our board of directors is composed predominately of doctors with the same problems, stresses and concerns as you.
- Because we support political action in matters of health care benefiting all Rhode Islanders.
- Because our bottom line is superior service.

Phone 272-1050 — ask for Shirley and
Learn How We Can Do It Better For You!

RIMS Insurance Brokerage Corporation
The Experts in Medical Liability Insurance

Now offering up to 2M/4M limits for select insureds.

Also offering workers' compensation.

RIMS Insurance Brokerage Corporation
One Hayes Street, Providence, Rhode Island 02908
Phone (401) 272-1050 FAX (401) 272-1051

COMMENTARIES

Modern Day Practice of Anesthesiology

Anesthesiology has made amazing strides in recent years. Much of this growth is the result of the ever increasing demands placed upon the specialty by the sophisticated surgical techniques that our colleagues undertake. We have taken some of the skills that we learned out of the operating room into other arenas, including clinics, to deal with acute and chronic pain management.

We are seeing sicker and older patients coming through for a variety of procedures from cataract extraction to open heart surgery. Anesthetic management certainly plays a key role in the successful outcome of the surgical procedure. The first step in anesthetic care of patients is a thorough preoperative evaluation. The patient must be in the best possible medical condition given the underlying disease process. Anesthesiologists have had to learn a great deal about modern medical management to make these decisions about optimal patient preparation. The next step is determining the optimal anesthetic course for the operation. It is clear that the anesthetic must be one that optimizes the ability of the surgeon to perform the desired procedure while respecting the patient's medical state. We have available to us new drugs and techniques which now enable us to have a wide variety of choices specific to these needs. In addition, we now take a more active role in the pain management of the patients during the post-operative period leading to earlier mobilization and fewer complications.

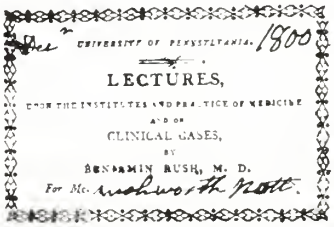
Anesthesiologists are proudest of the steps that we have taken as a specialty to ensure the safety of anesthetic care. Through research and development, technology for pulse oximetry to measure oxygen saturation and end-tidal capnography to measure expired carbon dioxide became available in the 1980s. Our national society did not just advertise that these modalities were available. The result of action on a national level was the establishment of monitoring standards to include the use of these new modalities. There has been a sharp decline in anesthesia mishaps resulting in hypoxic damage. Our malpractice premiums have declined reflecting this improvement. Some forward looking carriers have offered discounts in premiums to those anesthesiologists who routinely use these devices. The specialty of anesthesiology was the first to adopt such standards. Our national society is working for practice parameters in order to address two major areas of interest: the difficult airway and invasive central monitoring. It is hoped that by early and aggressive action in the area of practice parameters, we can again be trend setters.

Monitoring of the compromised patient has been another advancement. The use of the pulmonary artery catheter has taught us a great deal about the patient's physiological responses to anesthetic agents, surgical manipulations, fluid shifts, temperature changes, and possible cardiac ischemic events. On the horizon is more routine use of the esophageal Doppler which will help to define in more detail cardiac function in response to various surgical and anesthetic interventions.

Some of the traditional caveats in anesthetic care are being reevaluated. The use of inhalation agents in the face of hepatic dysfunction may be permissible. No oral intake after midnight may no longer be necessary or advisable. The effects of some anesthetics on the coronary circulation has raised the question of coronary steal. New non-opioid pain relievers are being used while others are being developed to maximize pain relief while minimizing respiratory depression. The paraspinal space has been used for injection of multiple agents to achieve pain relief. New drugs to replace older drugs with undesirable side effects are being closely evaluated. Replacements for succinylcholine and nitrous oxide are on the horizon.

It is hoped that this issue will provide some insight as to what goes on behind the closed doors of the operating room. We in Rhode Island are proud of the anesthesia services that we provide to our patients. We plan to improve on that care as technology and education progress.

Kathleen C. Hittner, MD
President
Rhode Island Medical Society
Chief of Cardiac Anesthesia
The Miriam Hospital


UNIVERSITY OF PENNSYLVANIA. 1800
LECTURES,
ON THE INSTITUTES AND PRACTICE OF MEDICINE
AND ON
CLINICAL CASES,
BY
BENJAMIN RUSH, M. D.
For Mr. Ashworth Mott.

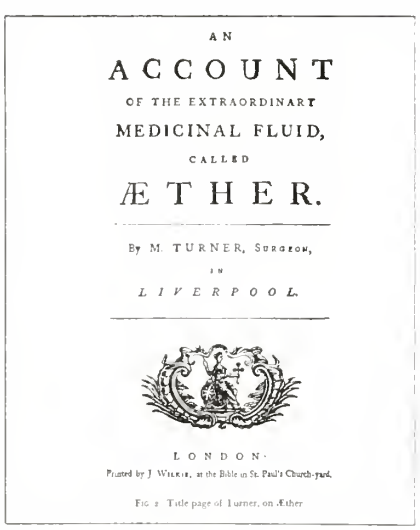
Photograph of a card of admission to the lectures of Benjamin Rush, issued in December, 1980.

This Priceless Gift to Humanity

"To goodness and wisdom," said Proust, "we make promises; pain we obey." No physical state, no terror of the mind, equals the human dread of acute physical pain. In medicine, the implacable enemy is not death but pain. And for millennia medicine has labored more to lessen pain than to lengthen life. First, do no harm, was always the prevailing imperative, but in truth, the first intervention customarily was to bring relief from pain.

The need to pacify pain compelled every past culture to explore its potential resources, and each culture independently managed to identify the pain-reducing effects of alcohol, as well as various botanical extracts from sources such as the poppy or mandrake. But none of these oral measures could suppress the terrible pain inflicted by the surgical knife. Surgery therefore languished until deep, reversible, insensible sleep could be willfully induced and interventions then undertaken with deliberateness and planning.

The discovery of inhalant anesthesia (variously ascribed to Logan, Wells, Morton, Bigelow, Warren and Jackson) should probably be assigned to the entrepreneurial dentist from Massachusetts, William Thomas Green Morton. On the evening of September 30, 1846, a Mr. Eben Frost, suffering from a remorseless toothache, sought Morton's professional help. Morton soaked a handkerchief with a colorless fluid, sulfurous ether, and had his patient inhale the volatile gas. Within minutes, Frost was unconscious and the tooth was extracted with relative ease – and without pain. After trying this new procedure upon a small series of dental patients, with moderate success, Morton applied to JC Warren, MD, surgeon to the Massachusetts General Hospital, to demonstrate upon a surgical patient, ". . . the preparation which I have invented to diminish sensibility to pain." (Morton kept secret the chemical nature of the inhalant substance, disguising its characteristic scent with aromatic perfumes, and calling it Letheon rather than by its generic name.) On October 16, 1846, the gas was administered to a Mr Gilbert Abbott, a young adult with a massive neoplasm at the angle of his jaw. After an estimated four minutes of inhalation (no one had bothered to time the induction) the patient was unconscious and Dr Warren proceeded to resect the tumor. In his journal, Warren later wrote, "A new era has opened on the operating surgeon. His visitations on the most delicate parts are performed, not only without the agonizing screams he has been accustomed to hear, but sometimes in a state of perfect insensibility and occasionally even with an expression of pleasure on the part of the patient."


AN

ACCOUNT

OF THE EXTRAORDINARY

MEDICINAL FLUID,

CALLED

ÆTHER.

By M. TURNER, Surgeon,

IN

LIVERPOOL.

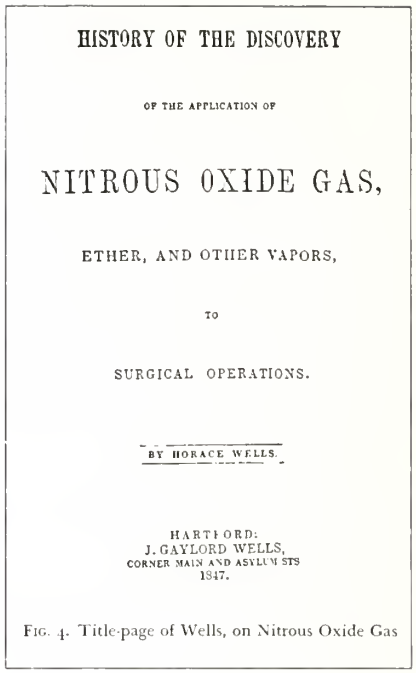
LONDON:

Printed by J. Wilkie, at the Bible in St. Paul's Church-yard.

Fig. 3. Title page of Turner, on Æther

History tells us precisely the very moment and the place for this uniquely momentous advance in the art of medicine. Indeed, the Boston amphitheater which witnessed this miracle, and is now called the ether dome, is an enshrined site. But it was the prior centuries of thinking, experimental and abortive efforts undertaken by others which finally allowed Morton and Warren to capitalize upon the unique properties of ether.

Ether (ethyl ether, $(C_2H_5)_2O$) is not found naturally but requires laboratory synthesis. Some dim references to ether are found in the alchemic literature of the middle ages, but the first publication detailing its preparation is found in the 1540 text, *De artificiosis extractionibus*, authored by Valerius Cordis. The process required the mixing of sulfuric acid with alcohol (sweet wine). The resulting fluid he called sweet vitriol. To this new substance, Valerius ascribed the following properties: " . . . it penetrates liquids; it is especially valuable for all putrefactions of the body; it draws the pus and mucous from the lung in pleurisy, peripneumonia and hacking cough, for it may be securely taken internally. It easily evaporates."


HISTORY OF THE DISCOVERY

OF THE APPLICATION OF

NITROUS OXIDE GAS,

ETHER, AND OTHER VAPORS,

TO

SURGICAL OPERATIONS.

BY HORACE WELLS.

HARTFORD:
J. GAYLORD WELLS,
CORNER MAIN AND ASYLUM STS
1847.

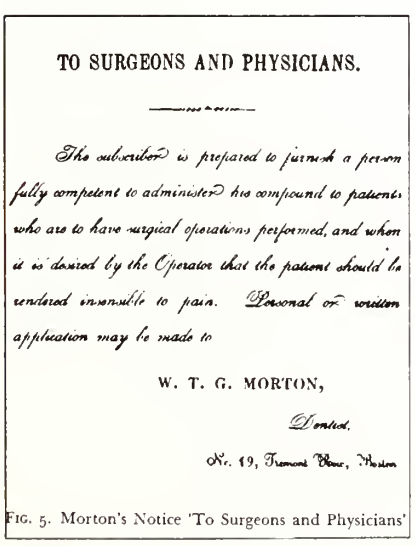
Fig. 4. Title-page of Wells, on Nitrous Oxide Gas

Experiments on the physicochemical nature of sweet vitriol are recorded by Robert Boyle (1680) and Isaac Newton (1704). In 1730, the German chemist Frobenius published an account of this substance which he renamed *spiritus vini aethereus*, and in English, sulfuric ether.

A treatise on ether and its medicinal qualities, authored by Matthew Turner, Surgeon of Liverpool, appeared in 1743. For the treatment of intractable headache, Turner recommends: "In stubborn Cases, it will likewise be serviceable to snuff a little of the AETHER up the Nostrils, either alone or in equal parts of Lavendar water, Hungary Water or Brandy; or it may be more convenient to apply a bit of Linen rag wetted with Aether, up the nostrils." This brief instruction appears to be the first published recognition that the medicinal properties of ether can be exerted through inha-

lation. Inhalation medicine (pneumatology), largely a British contrivance, was vigorously pursued during the following century by such scientists as Davies Gilbert, Humphry Davy, Henry Hickman and their students. Their scientific claim was to clarify the physiologic effects of various isolated gases upon the human organism, and to note whether any of these gaseous elements might possess some therapeutic value. The nature of respiration, the kinetics of gaseous exchange and the essentiality of oxygen were some of the scientific products of these inquiries. In terms of inhalant anesthesia, these collective studies demonstrated clearly that altered consciousness could be achieved by changing the gases inhaled. Ether, however, was not one of the substances tested.

During the early decades of the nineteenth century, nitrous oxide, and to a lesser degree, sulfuric ether, were widely employed as recreational drugs. Inhalation of either gas produced altered and pleasurably heightened sensations in those who briefly inhaled the volatile substances. Social parties were organized around the availability of these gases, the so-called ether frolics, but only the most perceptive noted that those who experimented with these gases became temporarily immune to incident pain. The curious effects of nitrous oxide gas ("laughing gas") were often exhibited in the side shows of carnivals and travelling circuses. Horace Wells, a dentist from Hartford, learned first about the mind-altering properties of nitrous oxide while attending a local circus. He then exploited its anesthetic qualities when he extracted teeth, following nitrous oxide inhalation, as early as December 11, 1844. Morton, a colleague of Wells, was sensitive to the humanitarian merit of inhalant gases as well as their immense commercial possibilities. Following a suggestion by Dr Charles Jackson that sulfuric ether might also serve this pain suppressing purpose, he tried ether upon Mr Eben Frost for tooth extraction and a short time later upon Dr Warren's patient, Gilbert Abbot, for general surgery. History gives credit to Morton for the discovery of ether as an anesthetic, since the ensuing publicity of the Abbott operation spread rappidly throughout both hemispheres and only then was ether rapidly adopted as an anesthetic agent. History also records the isolated activities of a physician in rural Georgia, Crawford W. Long, who used inhalant ether to resect a small tumor of the neck on March 30, 1482 – but he did not bother to announce his discovery to the scientific world. Only belatedly, after Morton's triumphs, did Long publish an apologetic summary of his limited experiences with ether.


TO SURGEONS AND PHYSICIANS.

The subscriber is prepared to furnish a person fully competent to administer his compound to patients who are to have surgical operations performed, and when it is desired by the Operator that the patient should be rendered insensible to pain. Personal or written application may be made to

W. T. G. MORTON,

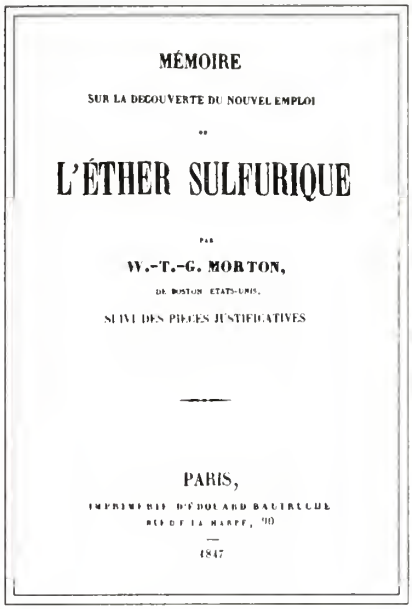
Dentist.

No. 19, Tremont Row, Boston.

FIG. 5. Morton's Notice 'To Surgeons and Physicians'

New England's Oliver Wendell Holmes, poet and surgeon, was humbled before "... this priceless gift to humanity; the fierce extremity of suffering has been steeped in the waters of forgetfulness, and the deepest furrow in the knotted brow of agony has been smoothed forever." In November of 1846, a few weeks after Morton's inaugural use of sulfuric ether, Holmes suggested a newly devised name for the process: *anaesthesia*, from the Greek, without sensation.

Most of the art and applied science of anesthesiology has developed in the United States. James Young Simpson, of Scotland, however, was responsible for the study and application of chloroform, particularly to obstetrical deliveries. When, many years later, Simpson was knighted, he adopted as his coat of arms the rod of Esculapius


MÉMOIRE

SUR LA DÉCOUVERTE DU NOUVEL EMPLOI

L'ÉTHER SULFURIQUE

PAR

W.-T.-G. MORTON,

DE BOSTON (ÉTATS-UNIS).

SUIVI DES PIÈCES JUSTIFICATIVES

PARIS,

IMPRIMERIE DE FOUCAULT ET BAUTRUCHE

RUE DE LA HARPE, 90

1847

and the words *Victo dolore*, victory over pain.

Stanley M. Aronson, MD

A Dramatis Personae for the World of Anesthesiology

Medicine owes much to the classical cultures of the northern Mediterranean. Medicine's transnational language maintains its stoutest roots in Latin and Greek, and even the dimly remembered cosmogonic mythology of these cultural forebears continues to mold the very words, texture and imagery of medicine. Listed below are some of the mythical persons and places which have found their way into the terminology of modern anesthesiology.

Lethe: Lethe, by some authorities, was thought to have mothered the Graces; and to the ancient Greeks she also symbolized oblivion. In the Underworld, the Kingdom of Hades was guarded by Cerberus the monstrous watchdog with perhaps fifty heads. Beyond the guarded gates of this Underworld flowed three rivers, the Acheron (with Charon as its ferryman), the Styx and the Lethe. The Lethe watered the margins of the Elysian Fields, and those who drank of its waters lost all prior memory and en-

tered then into oblivion. (Derivatives: words such as lethargy, latent and lanthanum. When Morton first used ether as an anesthetic in October, 1846, at Massachusetts General Hospital, he called the gas, Letheon.)

Hypnos: The Greek spirit of sleep, and the brother of Thanatos, Hypnos was frequently represented as a bird-like creature whose fluttering wings conferred sleep upon mortals. Both brothers lived in the underworld domain of Hades and it is said that both were fathered by Hades, one of the surviving sons of Chronus and the brother of Zeus. Others state that the parents of Hypnos were Erebus and Nyx. The Latin name for Hypnos was Somnus. Hypnos fathered a son, Morpheus. (Derivatives: hypnosis, hypnotherapy, somnolence, insomnia, somnambulist, etc.)

Morpheus: God of dreams and the only recorded son of Hypnos. More literally, Morpheus was the maker of shapes (ie, dreams). No mention, in the many genealogies, of the identity of his mother. (Derivatives: morphine, because of its sleep-producing characteristics; morphology, the science of shapes; metamorphosis, etc.)

Thanatos: The other son of Hades, ruler of the Underworld. When in the nether regions, Thanatos, god of death, is said to be winged – and in appearance indistinguishable from his brother Hypnos. But when he emerges into the world of the living, he dresses in black, holding a deadly sword in his right hand as he steals silently among those unaware of his proximity. The fateful decisions of this god of death are said to be irreversible, but there have been documented instances where circumstances have proven otherwise. When Alcestis, wife of the King of Pherae was about to be buried, Heracles wrenched Alcestis from the grasp of Thanatos and returned her to the arms of her grieving husband. (Derivatives: thanatology, euthanasia.)

Ether: In the very beginning, Hesiod tells us, there was only Chaos, limitless and unilluminated space. After much time Chaos conceived Erebus who, joining with the darkness, gave birth to Ether and Hermera, the spirits of that day. Yet others say that Chronus sired both Chaos, a spirit without ending or dimension, and Ether, the spirit of the serene and finite. In latter Grecian writings, Ether was more narrowly defined as the sublime reaches of the airs, the preserve of Zeus, and separable from the waters, the preserve of Poseidon. To this day Ether signifies the clear medium of the heavens. (Derivatives: ether, ethereal.)

As evolving humans we have inherited, like it or not, the beliefs, the perceptions, the flawed explanations assembled by those who came before us. Most of these cosmogonies now seem either quaint or scientifically indefensible. Yet we manage to preserve a story-fragment here, a name there, from the intellectual struggles of our predecessors. In a science as remorselessly modern as anesthesiology, it is worth noting that the primal whispers of Greek mythology can still be heard.

Stanley M. Aronson, MD

The Language of Epidemiology (VIII). Cumulative Incidence

Prevalence answers the isolated question: What proportion of a studied population carries a particular disease at a particular time? Incidence rate answers yet another question: What is the probability that a person, randomly chosen from an uninvolved population, will develop a particular disease sometime during a determined time interval?

In attempting to understand the distribution of disease in populations, a third question necessarily rises: What proportion of a studied population, unaffected at the onset of an interval of observation, will develop a particular disease after an extended time span? This new measure of human disease kinetics is called cumulative incidence (CI). It combines some of the operative features of the first two measures. It is quite similar to prevalence: they are both dimensionless proportions and both are customarily expressed as percentages. But prevalence is an instantaneous profile of the studied population while CI follows a cohort of people over an extended observation interval to determine what proportion, in aggregate, will develop whatever is the studied outcome, usually a disease. On the other hand, it is also somewhat similar to an incidence rate since it is a measure of transition from one physiologic state to another.

Consider an example: A cohort of workers in some industrial plant are all briefly exposed to some toxic agent. The extent of individual exposure will inevitably vary, but even if it should not, the outcome of this toxic contact, as with any biologic response, will surely vary. Some employees will develop early signs of disease; some may develop disease only after a lengthy interval; and some may never show a reaction to the exposure. Let us say that 100 employees had been transiently exposed. During the first month, 6 showed illness; during months 2 to 6, an additional 11 became ill; and during months 7 to 24 another 4 became ill. No illness ascribable to the toxin emerged beyond 24 months following exposure. The CI of toxic reaction during the 24 month observation interval, therefore, is 21/100 = 21%.

When a population is said to be exposed to some harmful agent (chemical, physical, infectious etc), the proportion exhibiting some definable outcome is thus called the CI. In a sense, therefore, CI is a prevalence stretched out in time.

The observation time for CIs is frequently determined by past experience with the agent. For example, prior observation has shown that over 98% of susceptible individuals exposed to hepatitis A virus (as in instances of food poisoning) will develop clinical hepatitis within 45 days. Accordingly, the CI of hepatitis for a cohort of exposed individuals uses an interval at least as long as 45 days as a practical measure. At times when the agent is infectious, the CI is called an attack rate, although it is not truly a rate. When the provoking agent is exposure to radiation or some toxic metal, the outcome may be some form of cancer

or degenerative neurologic disease, in which case the time interval of the CI, may be many decades.

Is there any arithmetic relationship between incidence rate (IR) and CI? A simple algebraic expression links the two – but only if two conditions prevail: first, if the IR is very low; and second, if the IR remains the same throughout the interval of observation. Then,

CI = IR x (no. years of observation)

Why must the IR be low for this simple algebraic relationship to prevail? Assume, for example, that the IR of sprained ankles in the student body of a particular college, numbering 1,000 students, is 5% per year (ie, each year, on average, 50 students in each 1,000 will sustain a sprained ankle.) At the end of four years, were we to use the formula above, the cumulative incidence of sprained ankles would be 50/1,000 x 4 = 20%. But let us look at the progression of these four years more closely. In year 1, 5% of the student body develops sprained ankles (ie, 50 students). During the second year, the at-risk population is now not 1,000 but 950 (since a student with a prior sprained ankle cannot be counted a second time in a cumulative incidence). Thus, the number of the sprained ankles in the second year is 950 x 5% = 48; similarly, the number in the third year is 902 x 5% = 45; and in the fourth year, 857 x 5% = 43. The cumulative incidence of four years, then, is 186 per 1,000 (18.6%) and not 200 per 1,000 (20%).

The algebraic recognition of the fact that a person can only be counted once in an aggregate, cumulative measurement of cases, such as CI, is expressed as follows:

$$CI = \frac{IR}{\frac{1}{\text{no. years}} + \frac{IR}{2}}$$

Stanley M. Aronson, MD

March, 1992, contents
RHODE ISLAND MEDICINE

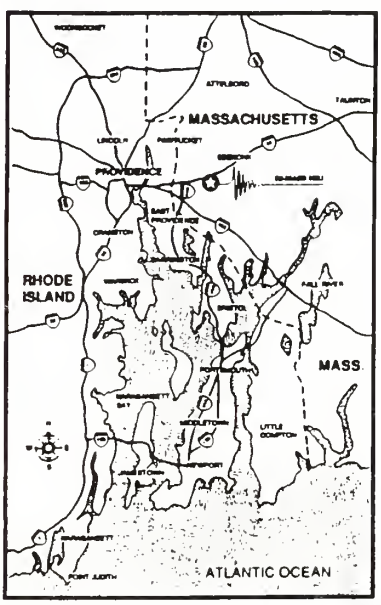
Ethical Issues in Medicine

Physician-Assisted Suicide
Suicide in Newport County
Breast Implants and their Risks
The Ethics of Research in Incurable Disease
Ethical Dilemmas of America's Health Care System

MAGNETIC RESONANCE IMAGING

RI-MASS MRI

309 Taunton Ave. (Rt 44), Seekonk, MA 02771



- Prompt Scheduling (within 24 hours)
- Pleasant Outpatient Setting
- High Quality Images (Sent to your office within 24 hours.)
- Latest Generation MRI Technology (3D and MR Angiography available)

RI-MASS MRI is a state of the art magnetic resonance imaging facility conveniently located on Taunton Avenue just blocks from the state line. To learn more about RI-MASS MRI or to receive more information about our facility (Rx pads, patient brochures, etc.) please contact Ruth Nash (Site Manager) at **1-800-848-9661.**

Patient Scheduling

1-(800)-848-9661

BURROUGHS WELLCOME COMPANY

Innovators in Anesthesia

is proud to support this special edition and acknowledge

Kathleen C. Hittner, MD
President
Rhode Island Medical Society
1991-1992

Richard Browning, MD
President
Rhode Island Society of Anesthesiologists
1990-1992

Marc Andreoni, MD
President
Rhode Island Society of Anesthesiologists
1992-1994

Pain Management: Trends in the 1990s

Gregory Towne, MD

Anesthesiologists have a long history of involvement with chronic pain management.

The past decade has seen significant advances in the management of pain. The recognition of current deficiencies in treatment has spurred the development of improved therapeutic modalities. Through the lay press, patients are better informed and request newer techniques to enhance their well being. The possibility of financial savings for hospitals, patients and insurers from reductions in complications and length of hospital stay has also been an incentive to ongoing exploration.

Anesthesiologists have a long history of involvement with chronic pain management. Despite a seemingly logical extension of their intra-operative role, only recently have they also become part of the acute pain management team. Their knowledge of the pharmacology of analgesics, pain pathways and regional anesthetic techniques is valuable in both of these areas. Presently in many institutions, anesthesiologists play an integral role in the multi-disciplinary approach to pain of all kinds.[1]

The actual physiologic events leading to pain perception after acute injury serve as the basis for therapeutic intervention. At the peripheral level, tissue damage leads to nociceptor (literally pain receptor) activation. Mediators of activation include potassium ions, bradykinin, and prostaglandins. Signals pass to the dorsal horn of the spinal cord via unmyelinated C fibers and thinly myelinated AΔ fibers. The cell bodies of afferent neurons synapse with ascending pathways in the spinothalamic tracts which proceed rostrally through the reticular activity system to thalamus and, ultimately, to cortex. Descending modulating pathways exist at several subcortical levels.

Paramount to successful pain management is the realization that coupled with these physiologic processes there is a psychologic component of pain. The underlying makeup of the patient, as well as the emotional implication associated with the injury, will profoundly influence the perception of pain. Additionally, this individual response pattern extends to pharmacokinetics and pharmacodynamics of analgesic medication, where wide inter-patient variability exists. Ultimately, our greatest discovery has been that individualization of pain therapy with ongoing evaluations and adjustments is the key to successful pain management.

Gregory Towne, MD, is Director, Anesthesia Pain Service, Department of Anesthesiology, Rhode Island Hospital, Providence, Rhode Island.

Opioid Analgesics

The opioid analgesics have been the mainstay of therapy for severe pain for nearly two centuries. It is now understood that their mechanism of action involves specific receptor sites within the CNS at both brain and spinal cord level. Many sub-types of these receptors are now recognized. Systemic administration of opioid analgesics results in an increased tolerance to pain with a seeming indifference to painful stimuli. Though opioids are effective analgesics, their use is limited by side effects, particularly respiratory depression. Other side effects include

ABBREVIATIONS USED:
CSF: cerebrospinal fluid
CNS: central nervous system
GABA: gamma amino butyric acid
ICU: intensive care unit
IM: intramuscular
IV: intravenous
NSAID: non-steroidal anti-inflammatory drug
PCA: patient controlled analgesic
PRN: pro re nata (as circumstances may require)
SC: subcutaneous
TENS: transcutaneous electrical nerve stimulation

sedation, decreased gastric motility, nausea, pruritis and urinary retention. It is important to note that studies have clearly shown that addiction is an extremely rare occurrence within the context of acute pain therapy with opioid analgesics.[2]

Traditionally, opioids have been administered for acute post-operative or post injury pain in a single fixed dosage PRN manner via the IM or SC routes. In theory, this supplies a depot of drug that maintains safe analgesic blood levels for several hours. Studies in the past two decades, however, have repeatedly demonstrated inadequacies with those modes of therapy. Drug absorption is erratic and unpredictable, leading often to low blood levels of short duration.[3] Several factors, including lack of knowledge of opioid pharmacology, and fear of side effects and addiction, have led physicians and nurses to routinely undermedicate patients.[4]

. . . patients are given access to a hand-held infusion device which allows delivery of small bolus doses of medication on a demand basis to maintain pain control.

The response to the inadequacies of traditional therapy has been the development of several innovations. Attempts have been made to manufacture a better opioid which would maintain analgesic effectiveness but limit side effects. Presently several agonist-antagonist and partial agonist agents exist. Claims of equivalent analgesia with limited or much reduced respiratory depression, however, remain unproven.

While awaiting the development of better agents, efforts have been directed toward using the established available agents more effectively. Opioids can be administered IV to address the inadequacies of IM and SC dosing. When given as a bolus, the rapid onset of action from quickly attained serum levels permits ready assessment of effect. Unfortunately, the rapid distribution also leads to a short half-life and requires frequent dosing. The logical solution to this problem is continuous IV infusion which can provide stable blood levels and is extremely effective. However, this technique generates appropriate concern about drug accumulation and potential toxic effects and requires enhanced monitoring for safe use. Therefore, despite its seeming suitability for regular use on in-patient wards, continuous IV infusion has been principally limited to use in intensive care settings.

Patient Controlled Analgesia (PCA)

An extension of IV bolus dosing is PCA. With this method, assessment of discomfort and response to therapy is performed by the patients themselves rather than care-givers. PCA involves use of a programmable, interactive infusion device. Following the initial establishment of analgesia, patients are given access to a hand-held infusion device which allows delivery of small bolus doses of medication on a demand basis to maintain pain control. Programmable features include individualized bolus doses, a "lockout" interval during which time additional doses cannot be given and a 4 hour limit on total dose. Additionally, separate from patient control, a small background infusion may be given. Care-giver evaluation allows for periodic adjustment of the various components. In this manner, patients are able to maintain adequate levels of analgesia with safety features which prevent overdosage. Side effects can be readily monitored on standard in-patient wards. Extensive experience with PCA at many institutions testifies to the overall safety of this method. Both patient and nursing satisfaction with PCA have been widely documented. Several studies have suggested improved patient outcomes with lower total narcotic dosage.[5,6] On-going investigation attempts to confirm that these improved outcomes can economically justify the cost of necessary equipment. Current trends suggest that PCA may well become the standard analgesic therapy for most acute pain over the next several years. PCA has also been used in the outpatient setting of chronic pain, typically oncologic, with excellent results.

Spinal Opioid Analgesia

In the mid 1970s, animal research demonstrated the presence of opioid receptors in the dorsal horn of the spinal cord. Subarachnoid and epidural block with local anesthetics had long been a technique employed for surgical anesthesia. The attendant sympathetic and motor denervation had limited its use for analgesia alone. Spinal opioids now offered the potential for selective analgesia.

Spinal analgesia refers to the drug administered via either the subarachnoid or epidural route. The most widely used is the epidural route which more readily allows for catheter placement and redosing. The opioid of choice is generally preservative-free morphine. The rich supply of receptors along with the pharmacokinetics of opioids at the spinal cord and CSF level allows for the achievement of profound analgesia with considerably less drug at more widely spaced intervals than would be possible with parenteral administration. Side effects are similar to the opioid side effects seen with many routes of administration. Of note, respiratory depression may be delayed as much as 18-24 hours due to slow cephalad distribution of drug to brain stem respiratory centers. Concern for this phenomenon has led to confinement of spinal opioids to the ICU setting for monitoring purposes. At present, a large body of evidence supports the safe use of this technique on regular wards, given proper patient selection and appropriate monitoring protocols.[11]

. . . spinal opioid analgesia has become established as a technique for the alleviation of many different types of acute and chronic pain.

Soon after the opioid receptors were demonstrated in animals, morphine was administered into the subarachnoid space of cancer patients with dramatic effects. Now, little more than a decade after its first clinical use in humans, spinal opioid analgesia has become established as a technique for the alleviation of many different types

of acute and chronic pain. Several studies indicate earlier ambulation and improvement in pulmonary function with the use of spinal opioid analgesia following thoracic and abdominal surgery.[7,8] Spinal opioids have also gained widespread use for post-operative analgesia following pelvic surgery and Cesarian section.[5] After lower extremity surgery, patients can benefit from earlier and more aggressive physiotherapy when their pain is treated with this technique.[10] For chronic pain, cancer patients can have epidural catheters implanted for long-term analgesia. Further application for this technique incorporates the concept of PCA via the epidural route.

On-going research is bringing the spinal application of opioid analgesics to ever expanding settings. Together with PCA, spinal opioid analgesia represents a real advance in the application of the opioid analgesics.

Non-Opioid Analgesics

Non-steroidal anti-inflammatory agents (NSAID) have long been used for pain associated with known inflammatory processes. Their mechanism of action involves inhibition of prostaglandin synthesis, preventing prostaglandin mediated enhancement of nociceptor activation at a peripheral level. Evidence also exists for prostaglandin activity at CNS sites, as well. These agents may be useful in conjunction with other agents, or as sole analgesic in certain types of pain with particular responsiveness to the NSAIDs, such as cancer pain secondary to bony metastases. A newly available parenteral NSAID, ketorolac, promises to expand the usefulness of this type of agent in acute pain settings.

Alpha-2 agonists are now under investigational use in both parenteral and spinal routes. Binding of alpha-2 receptors in the CNS leads to a decrease in catecholinergic output secondary to stressful stimulation. Norepinephrine is one of many neurotransmitters involved in the nociceptive response. Initial reports, particularly with spinally administered clonidine, suggested significant analgesia and reduction of opioid requirement. Early enthusiasm, however, has been tempered by the accompanying hypotension, bradycardia, and sedation seen with clonidine administration.[12] The utility of these agents will no doubt be further elucidated over the next decade.

Several other classes of non-opioid medications have been used for pain management purposes. Most of these have been employed in the chronic pain setting. Tricyclic antidepressants have wide utility for many different chronic pain situations. Their mechanism of action involves inhibition of serotonin and norepinephrine uptake centrally. By so doing, they modulate the pain signal as it travels to subcortical and cortical levels. Anticonvulsants are used for many neuropathic pain problems. Their effect appears to be mediated by membrane stabilization. Additionally, they may have an effect on the metabolism of the neurotransmitter gamma amino butyric acid (GABA).[13]

Regional Anesthesia

Regional local anesthetic blockade has been used for surgical anesthesia for over a century. Local anesthetics work at the level of the nerve axon, reversibly preventing action potential propagation. Analgesia is profound, as no painful stimulus can reach central processing areas. The attendant motor blockade has significantly limited itsusefulness in the management of the post-operative patient. Furthermore, as previously noted, spinal or epidural local anesthetic blockade is associated with sympathetic denervation which can have severe adverse hemodynamic consequences. Thus, modification of existing regional techniques is necessary before local anesthetic blockade can play a useful role in acute pain management. For example, use of lower concentrations of epidural local anesthetics, often in conjunction with opioids, may lead to profound analgesia without significant sensorimotor blockade. Additionally, some sympathetic blockade may be advantageous in certain situations. In patients who have had lower extremity surgery, a lower incidence of thromboembolic complications is demonstrable following local anesthetic blockade.[14] Other applications of regional blockade include brachial plexus blocks for upper extremity analgesia, and interpleural catheter techniques for thoracic or upper abdominal post-operative pain.

Miscellaneous Techniques

Several non-traditional methods for both acute and chronic pain therapy exist currently and are being studied for efficacy. One method developed in the 1980s and still used in some institutions is cryoablation. A cold inducing probe is placed directly on nerves in order to produce long-lasting sensory denervation. The technique produces anywhere from several days to several months of anesthesia. Its widest application has been for intercostal nerve block following thoracic or upper abdominal surgery. Initial enthusiasm has been tempered by side effects and problems with cost and technique. At present it remains of limited application.

Transcutaneous electrical nerve stimulation (TENS) is a method of pain control used extensively in chronic pain settings. The theoretical basis for this technique derives from the gate-control concept of pain. This suggests that inhibitory mechanisms within the spinal cord exist whereby non-noxious input can overwhelm the ability to interpret painful stimuli. Thus, the pain signal is interrupted. Several studies have attempted to show the utility of this method for acute severe pain.[15] Most, however, suggest that its effectiveness in this setting is limited.

Conclusion

Pain management allows anesthesiologists to use their unique knowledge and skills for consultation in an exciting, growing area of medicine. A multi-disciplinary approach has allowed us to better understand the nature of pain and the importance of individual assessment and treatment. The decade of the nineties will undoubtedly see on-going exploration and further innovations in this important area.

References

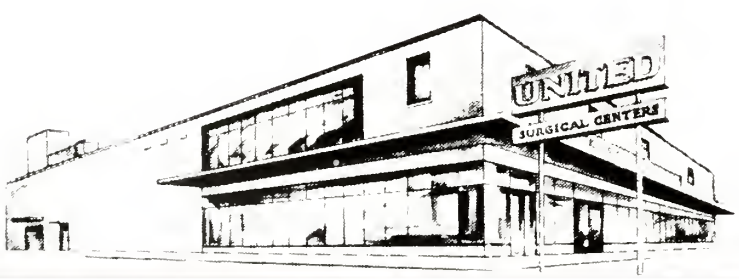
1. Ready BL, Oden R, Chadwick HS et al. Development of an anesthesiology based post-operative pain management service. Anesthesiology 68:100, 1988.
2. Porter J, Jick H. Addiction rare in patients treated with narcotics. NEJM 302:123, 1980.
3. Austin KL. Stapleton JW, Mather LS. Multiple intramuscular injections: A major source of variability in analgesic response to?. Pain 8:47-72, 1980.
4. Weis OF, et al. Attitudes of patients, housestaff and nurses toward post operative analgesic care. Anesth Analg 62:70-74, 1983.
5. Eisenach JC, Grice SC, Dewan DM. Patient controlled analgesia following Cesarean section: A comparison with epidural and IM narcotics. Anesthesiology 68:444-448, 1988.
6. White PG. Use of patient-controlled analgesia for management of acute pain. JAMA 259:243-247, 1988.
7. Rawal N, Sjostrand U, Christofferson E, et al. Comparison of intramuscular and epidural morphine for post op analgesia in the grossly obese: Influence on post-operative ambulation and pulmonary function. Anesth Analg 63:583, 1984.
8. Shulman M, Sandler A, Bradley J et al. Post thoractomy pain and pulmonary function following epidural and systemic morphine. Anesthesiology 1:569, 1984.
9. Bowen-Wright RM and Goroszeniuk T. Epidural fentanyl for pain of multiple fractures. Lancet 2:1033, 1980.
10. Gustafsson LL, Friberg-Nielsen S, Garle M. Extradural and parenteral morphine: Kinetics and effects in post-operative pain. A controlled clinical study. Br J Anesth 54:1167, 1982.
11. Ready LB, Lopez KA, Nessler M, Wild L. Postoperative epidural morphine is safe on surgical wards. Anesthesiology 75:3, 452.
12. Barnard JM, Hommenl Jl, et al. Post operative analgesia by IV clonidine. Anesthesiology 75:577-582, 1991.
13. Warfield CA, Stein JM, Frank HA. The effect of TENS on pain after thoracotomy. Ann Thorac Surg 39:462, 1985.
14. Modig J, Borg R, Karlstrom G, et al. Thromboembolism after total hip replacement. Role of epidural and general anesthesia, Anesth Anal 62:174, 1983.
15. Lee VC. Non-narcotic modalities for the management of acute pain. Anesth Clinics of NA 7:1, March 1989.

Address correspondence to:
Gregory Towne, MD
Department of Anesthesiology
Rhode Island Hospital
Providence, RI 02903

There must be a good reason why we've become the trusted back-up resource for more Rhode Island doctors (and their patients) than anyone else.

UNITED SURGICAL CENTERS

The Professionals in Home Health Care Equipment



We carry just about EVERYTHING for Home Health Care — which means, everything a patient or convalescent needs to implement the doctor's treatment directions. For Ostomy and Oxygen needs to Orthopedic Appliances, Wheelchairs, Walkers and Hospital Beds, we're here to serve your patients. Our staff is knowledgeable and dedicated to supplying exactly "what the doctor ordered." We've been doing it dependably for many years.

That's how we've earned the trust of so many doctors.

Medicare and Third Party Claims Accepted and Processed

380 WARWICK AVE., WARWICK
781-2166

NURSING PLACEMENT
HOME CARE INC.

"The 1st Choice in Certified Home Health Agencies"

We Are Proud To Announce:

NURSING PLACEMENT HOME CARE, INC.,
a **MEDICARE** and **MEDICAID CERTIFIED AGENCY.**

NPHC, the only letters that define Quality and Dependable Home Health Care in RI. Your patients deserve a choice and **NPHC** can offer them that – with a complete range of care options from Home Health Aides to Registered Nurses and all therapies.

We have provided your hospitals and private patients with quality care for 15 years and are now certified to serve all homebound patients in Rhode Island.

- RN assessments
- 24 hr. supervision
- RN
- HHA
- PT
- OT
- Speech
- MSW
- IV Therapy
- Pediatrics

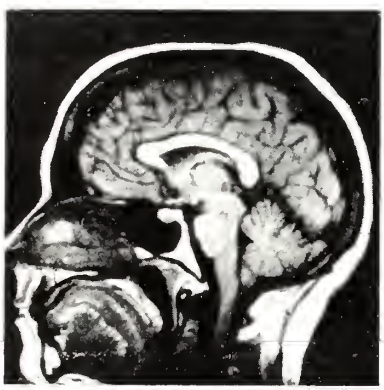
"For Home Care You Can Rely On"

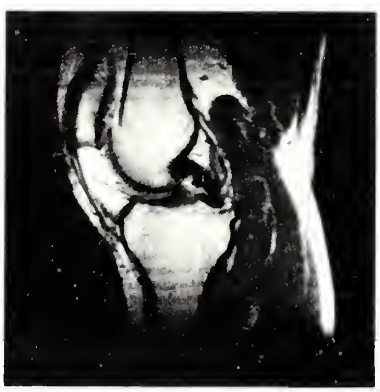
NPHC

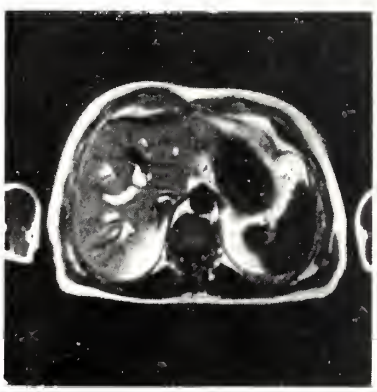
Please call 453-4474
1-800-287-2940

RI-MASS MRI, P.C. is pleased to sponsor the

2ND WEDNESDAY LECTURE SERIES







WHEN: The 2nd Wednesday
of each month
6:30 p.m. - 7:30 p.m.

WHERE: Marriott Hotel
Charles at Orms
Providence, RI 02904

THIS MONTH'S TOPIC:
"Knee and Wrist MRI: Current Experience"
Wednesday, February 12, 1992

NEXT MONTH'S TOPIC:
"Imaging of the Central Nervous System in AIDS"
Wednesday, March 11, 1992

TO REGISTER/CALL: 1 (800) 848-9661

Ambulatory Surgery: The Anesthesiologist as a Leader

John K. Hairabet, MD

...the anesthesiologist has emerged as the natural leader of the ambulatory surgical team.

Since early in this century, anesthesiologists have played a leading role in the development and provision of care to the surgical outpatient. In 1919, Dr Ralph Waters, a general practitioner and anesthetist established "The Downtown Anesthesia Clinic" in Sioux City, Iowa; the clinic offered complete operating room and anesthesia facilities for surgical and dental procedures. More recently, in 1969, two Arizona anesthesiologists, Fox and Reed, established the first successful surgicenter in Phoenix; it soon became the prototype of freestanding surgical facilities.[1-3]

During the past two decades, ambulatory surgery has changed from simple procedures performed on healthy young patients to complex procedures, under various anesthetics, in less than healthy or in elderly patients. It is estimated that within the next five years more than 60% of patients requiring surgery will undergo the procedure on an outpatient basis. Procedures such as cholecystectomy and hysterectomy have been performed on outpatients and freestanding recovery centers are being established for longer term ambulatory care. All of these developments demand from the anesthesiologist a greater participation in all aspects of the care of the ambulatory surgical patient.[4-5]

With the advent of modern anesthesia, and as medicine has shifted towards collective care of the patient, the anesthesiologist has emerged as the natural leader of the ambulatory surgical team. The 1990's anesthesiologist must distinguish himself by not only practicing the art of anesthesia, but also by demonstrating judgment, administrative skills, leadership in the operating room and a solid knowledge of basic sciences and medicine in general.[6]

Central to a successful ambulatory surgical program is an efficient preoperative patient evaluation and testing system . . .

Central to a successful ambulatory surgery program is an efficient preoperative patient evaluation and testing system in which the anesthesiologist must assume a leadership role to ensure that outpatients are appropriately selected, evaluated, tested, informed and prepared prior to the day of surgery. This will improve patient care by relieving anxiety, minimizing complications and avoiding cancellations and disruption of operating schedule.[7]

The Preoperative Anesthesia Clinic

The preoperative anesthesia clinic is one option to screening patients for ambulatory surgery. Depending upon the size of the facility and its caseload, the clinic is staffed by a secretary, registered nurses, laboratory and radiology technicians and an anesthesiologist. The anesthesia clinic visit is coordinated by the surgical scheduling office when the procedure is booked and must occur within a two week period prior to the date of surgery. Occasionally the clinic visit may be waived for out of town and nursing home patients, provided all necessary consultations and tests have been ordered by the surgeon with results available to the clinic staff on day of procedure when the patient is evaluated.[8]

With the rapid growth of ambulatory surgery there has been a continu-

ABBREVIATIONS USED:

ASA: American Society of Anesthesiologists

John K. Hairabet, MD, is Director of Anesthesiology at The Miriam Hospital and Clinical Assistant Professor of Surgery (Anesthesiology), Brown University, Providence, Rhode Island.

ous change for its indications, the range of acceptable procedures and types of patients. It is now established that patients of all ages, from neonates to octogenarians and ASA Class I to ASA Class IV stable patients may be acceptable for outpatient surgery.[9]

Following registration, the patient completes a health questionnaire which includes current illnesses, specific systems review, habits, allergies, medications and past anesthetics and surgical procedures. A nurse will then review with the patient all significant aspects of the medical history, institute perioperative teaching, familiarize the patient with the surgicenter routine, answer questions to relieve anxiety and give pertinent preoperative instructions. The patient is then interviewed and examined by the anesthesiologist who will request all appropriate consultations and laboratory tests, obtain informed consent for the anesthetic and order the preoperative medications. At this time the patient is given another opportunity to ask questions. All laboratory testing is performed and arrangements for consultations made by the staff prior to the patient's departure from the clinic.[10]

Routine laboratory testing is not the most effective way of evaluating the preoperative patient. Most studies indicate that about 60% of preoperative tests performed in the past could be eliminated without adversely affecting the outcome of surgery and anesthesia. Thus preoperative laboratory testing should be based on a complete history and physical examination rather than a predetermined list of tests.[10-12]

As soon as available all results and reports are reviewed by a clinic nurse who will report all significant abnormalities to the anesthesiologist who then determines if further testing or cancellation of the procedure is warranted. A timely review process and appropriate action will avoid surgical schedule delays on the day of surgery.

Preoperative and Anesthetic Care

Although small amounts of fluid taken on the day of surgery may not increase the risk of aspiration, all general anesthesia patients must abstain from solid food for six hours and liquids for four hours prior to induction of anesthesia. All others may take clear liquids up to four hours prior to procedure. The patient's medical regimen must not be disturbed and unless there is a contraindication all important medications must be taken on schedule with a small amount of water.[13]

Quality ambulatory anesthesia care will provide the patient with an anxiety free preoperative period, a smooth and safe intraoperative course and a comfortable pain-free postoperative recovery. All of the preceding may be achieved by carefully selecting the anesthetic technique and the rational use and judicious titration of anesthetic and analgesic drugs.

Premedicants are usually administered to produce anxiolysis, sedation and amnesia. Although the preoperative interview and instruction will decrease patient anxiety level, most outpatients will benefit from the preoperative use of a benzodiazepine and a short acting narcotic without increased recovery time. In selected patients who are at risk for aspiration premedication with a gastrokinetic in combination with an H2 antagonist will effectively reduce gastric volume, raise gastric pH and decrease the incidence of postoperative nausea and vomiting. Droperidol may be useful for outpatients undergoing procedures usually associated with high incidence of postoperative nausea and vomiting. Oral or intranasal midazolam is particularly effective in securing the cooperation of the pediatric outpatient.[14-19]

All outpatients should be monitored during the intraoperative and postoperative periods accordingtobasic monitoring standards recommended by the American Society of Anesthesiologists.[20-21]

The Anesthetic (General Anesthesia)

The ideal general anesthetic for outpatients should produce a rapid and smooth onset of action, intraoperative amnesia and analgesia, good surgical conditions, a short period of recovery and must be free of significant side effects.

In adults and older children, induction is usually accomplished with a rapid acting intravenous drug. Thiopental remains the most frequently used induction agent although propofol, a relatively new drug, is fast becoming popular in outpatient anesthesia because of its rapid elimination and low incidence of postoperative nausea and vomiting. In young children, mask induction with an inhalational agent is used.[22-23]

In adults and older children, induction is usually accomplished with a rapid acting intravenous drug.

Isoflurane alone or in combination with nitrous oxide may be used, although nitrous oxide has been implicated by association in the occurrence of post operative nausea and vomiting. Narcotic analgesics can also be used with or without nitrous oxide to maintain anesthesia. Shorter acting opioid analgesics such as alfentanil is recommended and can be administered intermittently or by continuous infusion and titrated to desired effect.[24-28]

Endotracheal intubation is employed when indicated by the type of surgical procedure or anytime that airway management by mask may be considered difficult. Succinylcholine remains the drug of choice to facilitate intubation, although other intermediate acting muscle relaxants, such as atracurium and vecuronium may be used in cases of longer duration.

Regional and Local Anesthesia

Regional anesthesia can be used for many outpatient surgical procedures. Regional anesthetic techniques avoid the use of general anesthesia and provide residual analgesic action in the postoperative period. Local anesthesia can also be used safely for a great number of procedures and is associated with the most rapid recovery. With both regional and local anesthesia the amount of local anesthetic used must be monitored to avoid anesthetic drug-induced toxicity.[29-30]

Conscious Sedation

Sedation is frequently desirable during local and regional anesthesia to relieve patient anxiety and produce amnesia and analgesia. This technique will achieve the desired effect without inducing general anesthesia. For ambulatory surgery it is important to elect a drug combination which has a rapid onset, short duration, rapid recovery and minimal respiratory depression; of the newer intravenous agents, propofol, midazolam and alfentanil seem to meet these criteria.[31-33]

Recovery from anesthesia

All patients recovering from anesthesia must routinely be monitored in a postanesthesia care unit. With the return of protective airway reflexes, consciousness, motor function and coordination, the patient may be gradually ambulated, provided the vital signs are stable and there are no apparent anesthetic side effects or complications. [34-37]

Most general anesthesia patients may be discharged two hours following the surgical procedure.

The most common early side effects following outpatient anesthesia include drowsiness, headache, sore throat, nausea and vomiting. Pain and inability to void are frequent problems in the immediate post operative period.[38-39]

Discharge Following Ambulatory Surgery

Most general anesthesia patients may be discharged two hours following the surgical procedure. Regional and local anesthesia patients may leave the facility within thirty to sixty minutes after surgery. Prior to discharge patients must meet conditions for safe discharge, be given verbal and written postoperative instructions and be accompanied by a responsible adult. A physician must be responsible for the discharge of the patient.

Conditions for safe discharge include stable vital signs, clear airway, absence of respiratory depression, awareness close to the preoperative level, ability to ambulate and perform activity close to preoperative levels, minimal nausea and vomiting with ability to take and retain oral fluids, ability to void and absence of excessive pain and other surgery related complications.

The anesthesiologist must assume an active role in the postanesthesia care unit ensuring safe patient recovery from the effect of the anesthetic, providing adequate postoperative pain relief and preventing and controlling postanesthesia nausea and vomiting. The anesthesiologist cannot control the complications of surgery, but can prevent or control postoperative side effects, thus playing a major role in curbing post ambulatory surgery hospital admission.[40-41]

Occasionally patients must be admitted to the hospital following outpatient surgery. Unexpected admissions may result not only from anesthetic related complications, but also from some preoperative medical condition, as well as surgery related events.[42-43]

Quality Assurance in Ambulatory Surgery

A useful tool in evaluating and improving ambulatory patient care is the routine follow up phone call by the nursing staff on postoperative day one. Patient responses and any postoperative complications must be documented and reviewed at regular intervals. In addition, a tracking system must be in place to detect and investigate all unexpected hospital admissions. The data obtained by the preceding methods must be periodically analyzed, errors corrected, and changes in policies and procedures, as well as technique instituted if indicated.

Conclusion

Having been accepted by the public, health care providers and third party payers, ambulatory surgery has become an integral part of medicine. To remain successful it requires appropriate selection and evaluation of patients, as well as continued development of anesthetic techniques and drugs designed to meet the needs of the modern age ambulatory surgical patient.

References

1. Water RM. The down-town anesthesia clinic. Am J Surg (Anes suppl) 1919; 33:71.
2. Reed WA, Ford JL. Development of an independent outpatient surgical center. Int Anesthesiol Clin 1976; 14(2):130.
3. Reed WA. Freestanding surgical care facilities. Int Anesthesiol Clin 1982; 20(1):109.
4. Wetchler BV (ed.) Outpatient Anesthesia. Churchill Livingstone, 1990.
6. Ring WH, Wong HC. Designing and administering an outpatient facility. In Problems in Anesthesia. Philadelphia, JB Lippincott, 1988.
7. Epstein BS. Controversial issues in ambulatory surgery. ASA Refresher Courses 1989; 17:531.
8. Apfeblaum JL. Preoperative evaluation, laboratory screening and selection of adult surgical outpatients in the 1990s. Anesthesiol Rev 1990; 17 (suppl 2):4.
9. Meridy HW. Criteria for selection of ambulatory surgical patients and guidelines for anesthetic management. A retrospective study of 1553 cases. Anes Analg 1982; 61:921.
10. Roizen MF. Preoperative patient evaluation. ASA Refresher Courses 1990; 216.
11. Turnbill JM, Buck C. The value of preoperative screening investigations in otherwise healthy individuals. Arch Intern Med 1987; 147:1101.
12. Roizen MF, Kaplan EB, Schreider BD et al. The role of history and physical examination and laboratory testing in preoperative evaluation for outpatient surgery: The "Starting Curve" of preoperative laboratory testing. Anesthesiol Clin North Am 1987; 5(1):15.
13. Schreiner MS, Treibwasser A, Keon TP. Ingestion of liquids compared with preoperative fasting in pediatric outpatients. Anesthesiology 1990; 72:593.
14. Shafer A White PF, Urquhart MC et al. Outpatient premedication: Use of madazolam. Anesthesiology 1989; 71:495.
15. Feld LH, Urquhart MC, Feaster WW et al. Premedication in children; oral versus intra muscular midazolam. Anesthesiology 1988; 69:745.
16. Lichter L, Dohrn C, Faure EAM et al. Effectiveness of premedication in anxious patients: does fentanyl or diazepam allay anxiety? 63rd Congress, IARS, 1989.
17. Coombs DW. Aspiration pneumonia prophylaxis. Anesth Analg 1983; 62:1055.
18. Ral TLT, Suseilar M, El Etr AA.

Metoclopramide and cimetidine to reduce gastric pH and volume. Anesth Analg 1984; 3:264.
[19] Dose VA, Shafer A, White PF. Nausea and vomiting after outpatient anesthesia effectiveness of droperidol alone or in combination with metoclopramide. Anesth analg 1987; 6:41.
[20] Standards for Basic Intra-operative Monitoring. ASA 1990 Director of Members: 640.
[21] Standards for Postanesthesia Care. ASA 1990 Directory of Members: 644.
[22] MacKenzie N, Grant IS. Comparison of the new emulsion formulation of propofol with methohexitone and thiopentone for induction of anesthesia in day cases. Br J Anaesth 1985; 57:725.
[23] Dose VA, Shafer A, White PF. Propofol versus thiopentalisoflurane for general anesthesia.
[24] Miur JJ, Warner MA, Buck CF et al. The role of nitrous oxide in producing postoperative nausea and vomiting. Anesthesiology 1986; 65:461.
[25] Korttila K, Hovorka J, Erkola O. Omission of nitrous oxide does not decrease the incidence of severity of emetic symptoms after isoflurane anesthesia. Anesth Analg 1987; 66:98.
[26] Wasudev G, Kambam JR, Hazlehurst WM et al. Comparative study of sufentanil and isoflurane in outpatient surgery. Anesth analg 1987; 66:186.
[27] White PF, Coe V, Shafer A, et al. Comparison of alfentanil with fentanyl for outpatient anesthesia. Anesthesiology 1986; 64:99.
[28] Zuurmond WWA, Van Leeuwenl A, Alfentanil V. Isoflurane for outpatient arthroscopy. Acta anesthesiol Scand 1986; 30:329.
[29] Mullroy M, Bridenbaugh LD. Regional anesthetic techniques for outpatient surgery. Woo SW (ed.), Ambulatory Anesthesia Care, Boston, Little Brown and Company, 1982:71.
[30] Bridenbaugh LD. Regional anesthesia for outpatient surgery. Can Anaesth Soc J 1983; 30:548.
[31] Philip BK, Supplemental medication for ambulatory procedures under regional anesthesia. Anesth Analg 1985; 64:1117.
[32] Negas JB, White PF. Use of sedative infusions during local and regional anesthesia – a comparison of midazolam and propofol. Anesthesiology 1988; 69:711.
[33] Kallar SK. Conscious sedation in ambulatory surgery. Anesthesiol Rev, 1990 (suppl II); 2:45-52.
[34] Steward DJ, Valgghi G. Stabilometry. A new tool for the measurement of recovery following general anesthesia for outpatients. Can anaesth Soc J 197878; 25:4.
[35] Enright AC, Pace-Floridia A. Recovery from anesthesia in out patients: a comparison of narcotic and inhalational techniques. Can Anaesth Soc J 1988; 24:618.
[36] Azar I, Karambelkan DJ, Lear E. Neurologic state and psychomotor function following anesthesia for ambulatory surgery. Anesthesiology 1984; 60:347.
[37] Korttila K, Valassal J. Recovery after outpatient isoflurane and enflurane anesthesia. Anesth Analg 1985; 64:239.
[38] Burns K. Postoperative care and review of complications. Ambulatory anesthesia Care, Woo SW (ed), Boston, Little Brown 1982:27.
[39] Heneghan C, McAuliffe R, Thomas D et al. Morbidity after outpatient anesthesia. Anesthesia 1981; 36:4.
[40] Wetchler BV. Problem solving in the post anesthesia care unit. Anesthesia for Ambulatory Surgery. 2nd edition, JB Lippincott, 1990.
[41] Patel RI, Hannaliah RS. Anesthetic complications following pediatric ambulatory surgery: a three year study. Anesthesiology 1988; 69:1009.
[42] Gold BJ, Kitz DS, Lecky JH et al. Unanticipated admission to the hospital following ambulatory surgery. JAMA 1989; 262(21):3008.
[43] Natof HE. Complication associated with ambulatory surgery. JAMA 1980; 244:1116.

A critical health problem for your patient. A difficult problem for you to treat.

The Miriam Hospital Weight Management Service offers treatment programs addressing all levels of obesity. With over 10 years' experience in obesity treatment and research, our multidisciplinary team provides the resources needed for safe, medically monitored weight loss and for long-term success in maintaining weight loss.

For more information on our programs, or to refer a patient, call:
(401) 861-0870

Portions of our programs may be covered by health insurance.

The Miriam Hospital Weight Management Service
Division of Behavioral Medicine
An affiliate of the Brown University Medical School

You treated little Johnny for measles in kindergarten, chicken pox in 3rd grade, mono in high school.

But what can you do for his HIV today?

People with HIV are special patients with specific needs. That's why it helps to have experience with HIV when treating an infected patient–the kind of experience doctors find at Clinical Partners.

Clinical Partners is a group of healthcare professionals dedicated to helping patients live with HIV. We are alone in the complete array of services we provide to physicians, employers and insurers of those living with HIV. Our early intervention averts costly hospital stays, while increasing patient care and support.

Operating successfully in Boston, New York and Los Angeles, Clinical Partners is pleased to announce the first anniversary of our Providence office, under the expert guidance of Linda Durand NP, RNC and Deborah Matson CISW, MSW.

We want Rhode Island physicians to know Clinical Partners is here to help, and here to stay. As the patient's primary physician, you can benefit from our knowledge and experience, which is available to help you treat HIV infection and AIDS.

To find out how Clinical Partners can be your partner in treating HIV patients, call our Providence office today at 454-8880 or 1-800-285-8880.

ClinicalPartners

Helping people make choices about HIV.

There's more to Portable X-Ray Service than X-Rays.

Yes, our main business is to provide you with fast, efficient, diagnostic X-Ray services, but we have much more to offer . . . including a staff of people who really care.

- Diagnostic X-Ray Services
- EKG
- Holter-Monitoring*
- Ultrasound Services*
- Same day reporting
- 24 Hour Service
- Seven days a week

*by appointment only

We service the entire Greater Rhode Island area:

• Nursing and Convalescent Homes • Shut-ins and Private Home Patients • Post Surgical Patients

PORTABLE X-RAY SERVICE

OF RHODE ISLAND

Certified by the R.I. Department of Health. Reimbursement provided by Medicare, R.I. Blue Shield and Medical Assistance.

100 Highland Avenue Providence, R.I. 331-3996	120 Dudley Street Providence, R.I. 331-3996	154 Waterman Street Providence, R.I. 273-0450	38 Hamlet Avenue Woonsocket, R.I. 766-4224

What Every Pediatrician Should Know About Pediatric Anesthesia

Richard Browning, MD
Andrew Triebwasser, MD
Alan J. Weissburg, MD

The scope of the pediatric anesthesiologist has expanded beyond the operating room, into the intensive care unit, the pain clinic and the respiratory therapy department.

Beginning in the early 1970s, pediatric anesthesiologists have become a distinct group of subspecialists providing perioperative care for children. A heterogeneous group, our ranks include veteran anesthesiologists who have acted on an affinity for children and have developed special clinical expertise, together with younger physicians who have completed one or more years of fellowship training beyond the basic residency program. Many of the latter group have also completed pediatric residencies and often function as liaisons between the two communities.

In addition to a more visible clinical profile, a steadily increasing stream of basic and clinical research has reached publication. This has transformed the subspecialty from an art based upon the experience of a few national authorities into an academic discipline in which methodology is subjected to scientific scrutiny and information is derived from objective study. At least one of the major American anesthesia journals has a special section on pediatric anesthesia,[1] and a journal dedicated strictly to pediatric anesthesiology is in its infancy. Textbooks dealing with pediatric anesthesiology have appeared which include several comprehensive works covering the entire field, to texts devoted to one special aspect of practice such as cardiac or regional anesthesia and pediatric intensive care. Within the American Academy of Pediatrics, the Section on Anesthesiology has grown to several hundred members, and under the umbrella of the American Society of Anesthesiologists, the Society for Pediatric Anesthesia, founded in 1985, has quickly become the academic focal point for practitioners across the country. The scope of the pediatric anesthesiologist has expanded beyond the operating room, into the intensive care unit, the pain clinic, and the respiratory therapy department.

Innovations instituted within the last several years include both conceptual and technical advances. The bulk of pediatric surgery has been shifted from the in-patient to the outpatient mode. Stress has been placed

Richard Browning, MD, is Chairman of the Department of Anesthesiology, Rhode Island Hospital and Clinical Assistant Professor of Anesthesia, Brown University, Providence, Rhode Island.

Andrew Triebwasser, MD, is Director of Pediatric Pain Service, Rhode Island Hospital and Clinical Assistant Professor of Anesthesia, Brown University, Providence, Rhode Island.

Alan J. Weissburg, MD, is Director of Pediatric Anesthesia, Rhode Island Hospital and Clinical Assistant Professor of Pediatrics and Anesthesia, Brown University, Providence, Rhode Island.

ABBREVIATIONS USED:

BPD: broncho-pulmonary dysplasia
CF: cystic fibrosis
CPK: creatine phosphokinase
CT: computerized tomography
ENT: ear, nose and throat
ET CO_2: end tidal CO_2
ICU: intensive care unit
IM: intramuscular
IV: intravenous
MRI: magnetic resonance imaging
NPO: nothing by mouth
SBE: subacute bacterial endocarditis
URI: upper respiratory infection
VSD: ventricular septal defect

on the importance of the child's psychological management during the perioperative period, including the use of sedatives and play therapy techniques for calming children, and an increasing place for parental participation during procedures. Concepts of the child's experience of pain have received much attention, especially with regard to the neonate. Newer agents, drugs, techniques and monitors have been introduced. The common denouement of all these changes has been increased safety and improved outcome. Finally, substantial efforts have been made to involve the resources of the primary care pediatrician in the provision of perioperative care.[2]

Although an exhaustive discussion of pediatric issues related to anesthesia is beyond the scope of this review, we have selected a cross section of pediatric anesthesia issues chosen to be of interest for the practicing pediatrician. Each is briefly reviewed below, and they include anesthesia safety and parental involvement, anesthesia and the neonate, the new anesthesia agents and monitors, the child as outpatient, the pediatrician as consultant, the alleviation of pain, and the use of sedation outside of the OR.

Anesthesia Safety and Parental Involvement

The two questions parents most frequently ask the pediatric anesthesiologist are "Is the anesthesia safe for my child?" and "Can we be there until the child is asleep?". As primary care physicians, you may also get these questions before we do. These are not simple questions to answer since the answer will vary from patient to patient and family to family.

. . . children younger than one month of age had the greatest risk of perioperative adverse events.

A few large scale reviews of anesthetic risk in children do exist and some conclusions can be drawn from them. A French study reviewed outcome data from over 40,000 anesthetics on children less than fifteen years of age. They found seven major complications per 10,000 cases within 24 hours of administration of an anesthetic.[3,4] This study, which indicates that major complications occur at a rate of once every 1,500 anesthetics, did not break the data down by age or site and severity of surgery. In 1990 a Canadian group reviewed the data from 1982-1987 at the Winnipeg Children's Hospital to determine the rates of perioperative adverse events occurring in children of different ages.[5] From their data reviewing 27,220 cases, children younger than one month of age had the greatest risk of perioperative adverse events. This age group had the highest incidence of major problems such as cardiac arrest and other cardiovascular, pulmonary and/or renal events. These infants were also much more likely to be undergoing major cardiovascular or intra-abdominal surgery and were likely to be sicker preoperatively than were the older children. Older children had fewer and less severe complications on average than newborns but still had complication rates higher than those reported for adults.

Overall, in comparison to adults, children were more likely to have nausea and vomiting, a higher incidence of respiratory problems and a significantly higher rate of recovery problems. When all of the events (major and minor) were considered, there was a risk of an adverse event in 35% of pediatric cases but only 17% with adult cases.

Armed with the above data, the pediatric anesthesia community has begun to address the incidence of adverse events with an eye to lowering them. The 1980s saw tremendous growth in the application of new technologies to anesthesia safety (these are discussed elsewhere in greater detail) and significant growth in the number of trained specialists in this field. The early data from these developments is encouraging. One set of authors has suggested that the application of current monitoring standards could reduce negative outcomes by approximately one-third.[6] Another group reviewing cardiac arrest data in infants reviewed outcome data from one institution over five years comparing anesthesiologists with and without pediatric fellowship training. The pediatric anesthesiologists had no cardiac arrests in infants whereas the rate for the other anesthesiologists was 19 arrests per 10,000 patients.[8]

. . . nausea and vomiting remain a significant problem for all children especially those older than five years of age . . .

When considering the safety issues for your patients, the following conclusions can be drawn: 1) neonates account for the highest morbidity rates; 2) there is a high incidence of respiratory difficulties in young children; 3) nausea and vomiting remain a significant problem for all children especially those older than five years of age; 4) children need a greater degree of vigilance and support in the recovery room and postoperatively; and 5) overall anesthesia safety is better than ever thanks to a combination of applied technology and specialty trained personnel. All of which confirms again what we as pediatricians already know. Children are not simply small adults. Children, therefore, require equipment specifically designed for and personnel specially trained for their unique requirements.

The second question which often comes fast on the heels of safety issues is whether or not the parents can be present during the anesthesia induction. The induction of anesthesia in the pediatric patient presents a unique challenge to the anesthesiologist. During this time, children are aware of the separation from their parents and that they are in a strange environment. In addition, they are not fully able to understand the necessity for their surgery, nor are they likely to be amenable to reasoned explanation.[8] Induction of anesthesia to a struggling or uncooperative child may produce unwanted physiological as well as psychological trauma to the patient.[9]

Unfortunately, the ideal induction techniques continue to elude us. An ideal technique would include a medication which was pleasant tasting,

available in a small volume, had a rapid onset producing unconsciousness, had a short duration of action and had no undesirable side effects. This kind of medication would allow for atraumatic separation from the parents, a smooth IV or inhalational maintenance of anesthesia and a rapid recovery from anesthesia. While we continue to search for such an agent, we as clinicians need to be aware of what options are currently available to best address the needs of our patients.

Induction of anesthesia to a struggling or uncooperative child may produce unwanted physiological as well as psychological trauma to the patient.

Since our patients are not only the children but also their parents, it is important to evaluate the psychological needs of both. The separation of the parent and child is often the most difficult part of the anesthesia experience. This may be minimized in one of two ways; either by allowing the parents to attend the induction,[10-12] or by the administration of a pre-medication which sufficiently sedates the child and then allows for an easy separation.[13-18]

The opinion among anesthesiologists has long been divided on whether parents should be in the operating room. This debate still continues across the country. Some studies have shown that parental presence at induction calmed the children and improved the induction for the child and the parents.[19] Others have found that parental presence at the induction is not always beneficial.[12] These latter authors contend that an attempt should be made to differentiate which parents will be helpful from those that will not be helpful during a pre-induction evaluation of parental anxiety.

An alternative to parental presence at routine anesthesia inductions (mask inhalation or IV) is to sufficiently sedate patients prior to the parental separation. Regimens including methohexital, pentothal, midazolam, diazepam, demerol, sufentanil chloral hydrate, ketamine as well as a few others, and combinations have all been recommended along with various routes of administration (ie, intramuscularly, rectally, orally, transmucosally and intranasally). Unfortunately, each drug and administration technique has some disadvantages. The barbiturates and some of the benzodiazepines tend to delay recovery and depending on route of administration, have highly variable times of onset. The narcotic medications are often associated with increased nausea and vomiting, decreased ventilatory compliance and irritation on administration. In addition, all of these techniques require additional trained personnel to assist in the administration of the drugs and the monitoring of these patients prior to their going to the operating room. In spite of the disadvantages, many of these techniques can be very anxiolytic to the children and their parents. This is especially true when appropriate pre-induction evaluation determines that such techniques would benefit both parent and child.

In conclusion, it is the feeling of these authors that either parental presence at induction or pre-induction medication regimens designed to facilitate separation are helpful to some parents and children. This is especially true of the children and parents of children in the 1-6 year age range. Therefore, it is important to organize the surgical suite to accommodate either or both of these needs without having to disrupt the operating room schedule or routine.

Anesthesia and the Neonate

Few conceptual aspects of perioperative care have undergone as profound a restructuring as the approach to anesthesia for the neonate. In years past, anesthetics had been withheld from sick neonates undergoing surgery in the belief that these patients were often too unstable to withstand the effects of such agents. Furthermore, it was purported that the nervous system of the neonate was insufficiently integrated or myelinated for the true perception of pain.[20] Recent research has demonstrated quite the opposite conclusion. Painful stimuli provoke cardiovascular, neurologic, behavioral and endocrine responses in neonates which can be significantly reduced by anesthetic agents.[21] In 1987 the American Academy of Pediatrics stated that the decision to reduce or withhold anesthetic or analgesic medication "should not be based solely on the infant's age or perceived degree of cortical maturity."

Inhalation anesthetics remain the mainstay for infants and vigorous neonates. For sick prematures, neonatal surgical emergencies such as congenital diaphragmatic hernia and infants with congenital heart disease, high dose narcotic anesthesia with agents such as fentanyl or sufentanil provide effective protection with a minimum of hemodynamic perturbation.

Regional anesthesia also has a place in the care of the neonate. Spinal, caudal and epidural anesthesia have been used as sole anesthetics in infants with chronic pulmonary disease and are frequently employed as adjuncts to general anesthesia and for postoperative pain control. Brachial plexus block has been employed for similar situations and also to treat vascular insufficiency following major hand surgery.[22] The use of penile block for routine neonatal circumcision[23] has been shown to be of great benefit as has the use of local anesthetics for procedures such as lumbar puncture, bone marrow aspiration and the insertion of venous or arterial catheters.

New Agents

Inhalation anesthetics remain the workhorse of the pediatric anesthesiologist's stable. The use of these agents is continuously refined as research efforts further explore their mechanisms and effects. Halothane is still the most commonly used agent in children for inhalation induction of anesthesia but isoflurane has in many institutions surpassed halothane as a maintenance agent. Two new and as yet unreleased agents, desflurane and sevoflurane, possess properties which may bring them to the forefront of pediatric anesthesia practice.

Propofol is a unique intravenous anesthetic which features a remarkably quick recovery period and seems especially useful in outpatient surgery.

Its use as a sole agent or in low doses as a sedative for children is currently being explored.[24] Ketamine's role in pediatric anesthesia is expanding. It can be used as an anesthetic or sedative and may be given by the oral, rectal, nasal or IM or IV routes. The new benzodiazepine midazolam, also produce useful sedation in any of the above routes and may be combined with other agents. The oxybarbiturate, methohexital, may also be given via the rectal route to induce anesthesia without needles or face masks.

Newer muscle relaxants in the curare class have been introduced and have largely replaced older agents such as d-tubocurarine and gallamine. Drugs of this nature are extremely important anesthetic adjuncts. Agents such as atracurium, vecuronium, doxycurium, pipecuronium and mivacurium provide an array of duration of action and route of elimination, and near absence of hemodynamic side effects.

As discussed earlier, renewed interest in pediatric pain control has resulted in increased use of narcotic[25] and non-narcotic analgesics. Older drugs such as morphine and meperidine are being used more aggressively via the oral, epidural or intrathecal routes. The usefulness and versatility of methadone has become apparent. Fetanyl, sufentanil and alfentanil have numerous uses in the operating room, post anesthetic care unit and ICU. Non-narcotic analgesics such as ibuprofen are being used in the pediatric age group, and the recently introduced ketorolac, the first parenteral non-steroidal anti-inflammatory drug is being investigated for use in children. This drug is an extremely potent analgesic which lacks the side effects of opioid compounds.

Newer Monitors

It is doubtful that any monitoring device has gone from introduction to ubiquity as quickly as the pulse oximeter. Together with the capnometer, pulse oximetry has led to documented improvements in OR safety which have been reflected in reduced malpractice premiums. Despite their expense, their use is now mandated by the American Society of Anesthesiologists.

The pulse oximeter[26] consists of a sensor and microprocessor. The sensor contains a light-emitting diode which shines both red and infra-red light across any pulsating capillary bed toward a light detector. The amount of light detected will fall cyclically as a pulse of arteriolized blood moves through the capillaries absorbing additional light. The ratio of red and infrared light absorbed will vary directly with the ratio of oxyhemoglobin and deoxyhemoglobin in the capillary blood at that moment. The microprocessor is able to follow changes of ratio from microsecond to microsecond and display the percentage of oxyhemoglobin in the capillary blood at the moment of greatest light absorption. This number will correspond to the oxygen saturation of arterial blood with striking accuracy. Factors which will distort this data are well described and are easy to avoid, making this device non-invasive, safe and reliable in the real-time display of a clinical indicator of universal value.

Together with the capnometer, pulse oximetry has led to documented improvements in OR safety.

To the pediatric anesthesiologist, the capnometer[27] which measures the percentage of carbon dioxide in respiratory gas is an equal partner to the pulse oximeter in the perioperative management of children. The last few milliliters of gas expired at the end of tidal breathing is virtually pure alveolar gas, the CO_2 content of which is nearly identical with arterial CO_2 tension. Since end-tidal CO_2 is the end result of processes which begin at the cellular level and depend upon intact pulmonary circulation and unobstructed gas flow within the airway, this monitor will reflect abnormalities anywhere along this pathway. Capnometry will detect esophageal intubation, kinked or blocked endotracheal tube, pulmonary embolus or decreased cardiac output by displaying reduced or absent levels of end tidal CO_2. Hypoventilation or the malignant hyperthermia syndrome will manifest increased $ETCO_2$. Clinicians can diagnose numerous other conditions from analysis of the capnographic tracing.

Other monitoring devices which have had significant impact on the anesthesiologist's practice include automated non-invasive blood pressure measurement and electronic thermistors for improved temperature control. Hemoglobinometers and glucosometers which require but a drop of blood are available in the OR. In the future, transesophageal echocardiography and processed electroencephalography may further refine perioperative care.

The Child as an Outpatient

Despite general agreement that outpatient surgery provides overall psychologic benefit, it uniquely stresses the family and raises significant questions about how to best deal with these stresses. Many surgical units provide preoperative visits for children, offering supportive services such as videos, coloring books, pamphlets, and rewards such as stickers, cartoon character band-aids and certificates. We generally endorse an honest approach with children, and encourage them to ask questions; many fears are based on misconceptions and are easily alleviated.

The preoperative fast, long regarded as a necessary evil, has recently undergone a major face lift. We still require an overnight fast for solids and milk products but now permit clear fluids in unlimited quantity up to two hours prior to surgery.[28] Although the most obvious benefit in this approach is that of psychologic well-being with less hunger, possible additional benefits include metabolic homeostasis, hemodynamic stability under anesthesia, and improved postoperative tolerance of feeding resumption.[29] These certainly deserve further study.

The Pediatrician as Consultant

With the increasing complexity of medical problems with which children are being admitted for same-day surgery, greater demands are placed on the pediatrician to provide family guidance as well as information for the

surgeon and anesthesiologist regarding a patient's condition and suitability for outpatient surgery. However, a recent study revealed that many pediatricians know little regarding perioperative anesthetic techniques, and unfortunately, view the anesthesiologist as being inaccessible.[30] The anesthesia department can promote efficiency and a more appropriate collegial relationship with primary care physicians through preoperative clinics, telephone consultations, grand rounds discussions, and an overall willingness to discuss a child's situation with surgeons, pediatricians and parents.

As primary care physicians, the pediatrician can ensure that children with underlying diseases are optimally prepared for surgery. In most cases, this merely involves instructing parents to continue prescribed medications through and including the morning of surgery. Certain situations might dictate "stress" doses of medications, such as preoperative corticosteroids for children who are steroid dependent or those who intermittently require steroids for bronchial asthma. The preoperative preparation might also include obtaining drug levels for children on chronic medications such as theophylline, digoxin, and anticonvulsants, with appropriate adjustments in dosing made prior to surgery.

The child with complex congenital heart disease should have a summary referral letter from his/her cardiologist, including past corrective surgery, results of recent investigations (such as cardiac catheterization and echocardiography) and often includes specific recommendations for perioperative SBE prophylaxis and arrhythmia control. Even children with uncomplicated heart murmurs may be candidates for SBE prophylaxis, and the pediatrician should distinguish between the child with a functional heart murmur and the child with, for example, a VSD or mitral valve prolapse. Oral SBE prophylaxis may be prescribed, as well, as per recommendations from the American Heart Association.[31]

Although a complete review of preoperative assessment is clearly impossible within this overview, one other situation merits brief mention. The child with Trisomy 21 is at risk for cervical spine injury due to atlantoaxial instability, and recent flexion-extension films of the cervical spine are necessary prior to anesthesia.[32-33]

. . . children with neuromuscular disorders may be predisposed to malignant hyperthermia . . .

Another area of concern is the child who has had prior difficulty with anesthesia, or in whose family there is a history of anesthetic mishap. The pediatrician can facilitate the appropriation of medical records which, by clarifying past events, will allow formulation of an anesthetic plan aimed at avoiding repetition of these problems. In particular, children with neuromuscular disorders may be predisposed to malignant hyperthermia and/or problems with administration of succinylcholine, and results of prior testing, such as muscle biopsy and CPK levels, should be available.

Many children present for surgery with symptoms such as nasal congestion and a dry cough. Indeed, for many children with ENT complaints, these symptoms will never completely resolve prior to surgical intervention. It has been long felt that the child with a clinical URI may undergo a stormier perioperative course, with more frequent episodes of arterial desaturation, laryngospasm, atelectasis and unexplained temperature elevation. However, there is a growing body of evidence that children with uncomplicated upper airway congestion can undergo general anesthesia with a complication rate similar to that of "healthy" controls, especially if the surgery is peripheral and anesthesia is achieved without endotracheal intubation.[34] Children with underlying cardiorespiratory problems (eg, CF, asthma, BPD) and those with fever, lethargy, poor appetite, productive cough or adventitious lung sounds should probably have elective surgery postponed at least two weeks following recovery to baseline.

Alleviation of Pain

Childhood pain has long been misunderstood and undertreated.[35] The reasons for this are complex, and include lack of familiarity with opioid analgesic pharmacology in children, fear of addiction, fear of side effects, and inadequate tools for assessment of pediatric pain. The complete anesthetic plan for an operation takes into account not only rendering the child insensate to operative trauma, but providing a reasonable plan for postoperative analgesia.

Even young infants are candidates, with appropriate surveillance, for techniques such as opioid infusions, caudal block, and spinal opioids.[25,36-37] The majority of pediatric surgical patients undergo neural blockade, either central or peripheral, as a component of "balanced" general anesthesia.[38] In some cases, this may be as simple and non-invasive as requesting the surgeon to infiltrate the edges of incision with bupivicaine, a local anesthetic of relatively long duration. As opposed to the usual practice with adult patients, in virtually all children, placement of nerve block or indwelling epidural catheter is made with the patient under general anesthesia. At our institution, we allow epidural (caudal or lumbar route) infusions of opioids on all pediatric patient care units, and infusions of epidural local anesthetics in the ICU. Furthermore, patient controlled analgesia devices will be instituted for children as young as seven years of age. This is a technique particularly suited to an adolescent's strong desire for autonomy, and allows for pretreatment of painful procedures or orthopedic manipulations.

The Anesthesiologist Providing Sedation Outside the OR

One area that is perhaps uniquely the domain of pediatric anesthesiologists is the provision of sedation and monitoring in such locations as CT scan, MRI scan and radiation therapy. Although a typical child will be suitably motionless with a combination of teaching, chloral hydrate, and restraints, approximately 15% of children may require additional sedation. Administration of hypnotic drugs with

the potential for respiratory depression to an inappropriately monitored child may lead to disastrous results.[39] An anesthesiologist can provide conscious sedation or at times, general anesthesia, with appropriate airway control and surveillance.[40] Short-acting agents such as fentanyl, midazolam, ketamine, thiopental and propofol can often obviate the need for prolonged recovery time. The specific agents used and route of administration are dictated by the individual patient's needs, and dosage titrated accordingly. NPO recommendations and monitoring are per standards established in the operating theater.

Conclusion

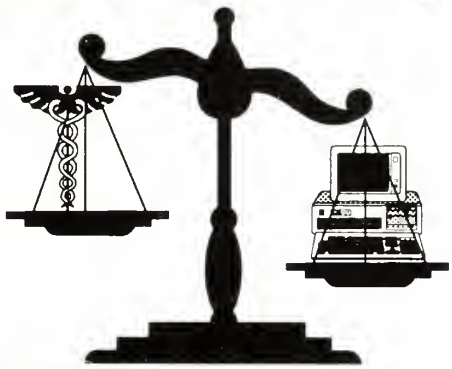
The pediatric anesthesiologist of today sees himself not only as a specialized anesthesiologist but also as a specialized pediatrician, much like a pediatric hematologist, nephrologist or cardiologist. Many of the changes and improvements noted in this review reflect this dual perspective. It is our intention to continue to improve this collaboration of medical disciplines through service, teaching and research in order to optimize the outcome of children's surgical experiences.

References

1. Anesthesia and Analgesia 73:1, July 1991.
2. Fisher QA: Clear for Surgery. Current Attitudes and Practices for Pediatricians. Clinical Pediatrics 30:1 January 1991.
3. Tiret L, Desmonts JM, Hatton F, Vourc'h G. Complications associated with anesthesia: a prospective survey in France. Can Anaesth Soc J 33:336-344, 1986.
4. Tiret L, Nivoche Y, Hatton F, et al. Complications related to anesthesia in infants and children: a prospective survey of 40,240 anaesthetics. Br J Anaesth 61:263-269, 1988.
5. Cohen MM, Cameron CB, Duncan PG. Pediatric anesthesia morbidity and mortality in the perioperative period. Anesthe Analg 70:160-167, 1990.
6. Tinker JH, Dull DL, Caplan RA, Ward RJ, Cheney FW. Role of monitoring devices in prevention of anesthetic mishaps: a closed claims analysis. Anesthesiology 71:541-546, 1989.
7. Keenan RL, Shapiro JH, Dawson K. Anesthetic catastrophe. APSF Newsletter, page 37, 1990-91.
8. Korsch BM. The child and the operating room. Anesthesiology 431:251-257, 1975.
9. Eckenhhoff JAE. Relationship of anesthesia to post-operative personality changes in children. Am J Dis Child 86:587-591, 1953.
10. Schofield N McC, White JB. Interrelations among children, parents, premedication and anesthetists in paediatric day stay surgery. Br Med J 299:1371-1375, 1989.
11. Page B, Morgan-Hughs JO. Behaviour of small children before induction. Anaesthesia 45:821-825, 1990.
12. Bevan JC, Johnston C, Haig MJ, Tousignant G, Lusy S, Kirnon V, Assimes K, Carranza R. Preoperative parental anxiety predicts behavioural and emotional responses to induction of anesthesia in children. Canadian J Anaesthesia 37(2):177-182, 1990.
13. Wilton NCT, Leigh J, Rosen DR, Pandit UA. Preanesthetic sedation of preschool children using intranasal midazolam. Anesthesiology 69:972-975, 1988.
14. Nelson PS, Streisand B, Mulder SM, Pace NL, Stanley TH. Comparison of oral transmucosal fentanyl citrate and an oral solution of meperidine, diazepam and atriopine for premedication in children. Anesthesiology 70:616-621, 1989.
15. Hanallah RS, Patel RI. Low-dose intramuscular ketamine for anesthesia preinduction in young children undergoing brief outpatient procedures. Anesthesiology 70:598-600, 1989.
16. Feld LH, Negus JB, White PF. Oral midazolam preanesthetic medication in pediatric outpatients. Anesthesiology 73:831-834, 1990.
17. Henderson JM, Brodsky DA, Fisher DM, Brett CM, Hertzka RE. Preinduction of anesthesia in pediatric patients with nasally administered sufentanil. Anesthesiology 68:671-675, 1988.
18. Spear RM, Yaster M, Berkowitz ID, Maxwell LG, Bender KS, Naclerio R, Manolio TA, Nichols DG. Preinduction of anesthesia in children with rectally administered midazolam. Anesthesiology 74:670-674, 1991.
19. Hanallah R, Rosales JK. Experience with parents' presence during anaesthesia induction in children. Can Anaesth Soc J 30:286-289, 1983.
20. Statement of the American Academy of Pediatrics. Pediatrics 80:3, September 1987.
21. Owens ME. Pain in infancy: Conceptual and methodological issues. Pain 20:213-230, 1984.
22. Audenaert SM, Vickers N, Burgess RC. Axillary block for vascular insufficiency after repair of radial club hands in an infant. Anesthesiology 74:368-370, 1991.
23. Stang JH, Gunnar M, Snellman L, et al. Local anesthesia for neonatal circumcision. Effects on distress and cortisol response. JAMA 259:1507-1511, 1988.
24. Westren P. The induction dose of propofol in infants 1-6 months of age and in children 10-16 years of age. Anesthesiology 74:455-458, 1991.
25. Yaster M, Deshpande JK. Management of pediatric pain with opioid analgesics. J Pediatrics 113:421-429, 1988.
26. Brown M, Vender JS. Non-invasive oxygen monitoring. Critical Care Clinics 4:3, 1988.
27. Stock MC. Noninvasive carbon dioxide monitoring. Critical Care Clinics 4:3, 1988.
28. Schreiner MS, Triebwasser A, Keon TP. Ingestion of liquids compared with preoperative fasting in pediatric outpatients. Anesthesiology 72:592-597, 1990.
29. Cote CJ. NPO after midnight for children–a reappraisal. Anesthesiology 72:589-592, 1990.
30. Fisher QA. "Clear for Surgery": Current attitudes and practices of pediatricians. Clinical Pediatrics 30:35-42, 1991.
31. Report of the Committee in Infectious Diseases: American Academy of Pediatrics (Red Book):538-543, 1991.
32. Pueschel SM, Scola FH. Atlanto-axial instability in individuals with Down Syndrome: epidemiologic, radiographic and clinical studies. Pediatrics 80:555-560, 1987.
33. Williams JP, Sommerville GM, Miner ME, et al. Atlanto-axial subluxation and Trisomy-21: Another perioperative complication. Anesthesiology 67:353-354, 1987.
34. Tait AR, Knight PR. The effects of general anesthesia on upper respiratory tract infections in children. Anesthesiology 67:930-935, 1987.
35. Schecter NL. Undertreatment of pain in children: An overview. Ped Clin NA 36:781-784, 1989.
36. Hertzka RE, Fisher DM, et al. Are infants sensitive to respiratory depression from fentanyl? Anesthesiology 70:213, 1989.
37. Taylor G, Boswell M. Continuous epidural infusion of low dose morphine for postoperative analgesia in children. AAP Spring Session, March 1991.
38. Yaster M, Maxwell L. Pediatric regional anesthesia. Anesthesiology 70:324, 19898.
39. Yaster M. Fetanyl-midazolam intravenous sedation in children: Case report of a respiratory arrest. Pediatrics 86:463-467, 1990.
40. AAP. Committee on Drugs and Section on Anesthesiology. Guidelines for the elective use of conscious sedation, deep sedation, and general anesthesia in pediatric patients. Pediatrics 76:317-321, 1985.

Address correspondence to:
Alan Weissburg, MD
Department of Anesthesiology
Rhode Island Hospital
Providence, Rhode Island 02903

BALANCE THE MEDICAL SIDE OF YOUR PRACTICE WITH THE BUSINESS SIDE



Vanguard Medical Management Services gives you and your staff more time for the medical side of your practice.

You love medicine. You and your staff are devoted to providing the best patient care possible. But, the business side of your medical practice is becoming more and more demanding. Frequent and complicated changes in medical insurance claims processing and accounting procedures are pulling your office staff away from medical and patient care services over to the business side of your practice. Maybe it's time to add a medical management service to your practice.

Vanguard Medical Management Services offers a comprehensive practice management service designed to free you and your office staff from time-consuming accounting and claims processing chores, plus provides qualified office staff for short, long-term and permanent assignments. Our team of experienced professionals help you and your staff manage the business side of your practice more efficiently, giving you more time to devote to your patients. You can trust us to provide:

- ✔ *Guarenteed revenue maximation*
- ✔ *Fast, accurate electronic claims processing for commercial insurance carriers, Blue Shield, HMOs, Medicare and Medicaid.*
- ✔ *A knowledgeable service representative dedicated to your practice*
- ✔ *Professional accounting/payroll services*
- ✔ *A confidential evaluation of your fee schedules*
- ✔ *Permanent and temporary staffing services*
- ✔ *Courteous, understanding and helpful response to your patients' billling questions.*

Call Geri Matraia at **(508) 842-4947** or **1(800) 743-2888** for information about putting **Vanguard Medical Management Services** to work for your practice.
New client consultations are free.

512 West Main Street, Shrewsbury, MA 01545

ONLY ONE H_2-ANTAGONIST HEALS REFLUX ESOPHAGITIS AT DUODENAL ULCER DOSAGE. ONLY ONE.

Of all the H_2-receptor antagonists, only Axid heals and relieves reflux esophagitis at its standard duodenal ulcer dosage. Axid, **150** mg b.i.d., relieves heartburn in **86%** of patients after one day and **93%** after one week.[1]

AXID®
nizatidine
150 mg b.i.d.

ACID TESTED. PATIENT PROVEN.

1. Data on file, Lilly Research Laboratories

See accompanying page for prescribing information

© 1991, ELI LILLY AND COMPANY

NZ-2947-B-249304

AXID®

nizatidine capsules

Brief Summary. Consult the package insert for complete prescribing information.

Indications and Usage: 1. *Active duodenal ulcer*– for up to 8 weeks of treatment at a dosage of 300 mg h.s. or 150 mg b.i.d. Most patients heal within 4 weeks.

2. *Maintenance therapy* – for healed duodenal ulcer patients at a dosage of 150 mg h.s. at bedtime. The consequences of therapy with Axid for longer than 1 year are not known.

3. *Gastroesophageal reflux disease (GERD)*– for up to 12 weeks of treatment of endoscopically diagnosed esophagitis, including erosive and ulcerative esophagitis, and associated heartburn at a dosage of 150 mg b.i.d.

Contraindication: Known hypersensitivity to the drug. Because cross sensitivity in this class of compounds has been observed, H_2-receptor antagonists, including Axid, should not be administered to patients with a history of hypersensitivity to other H_2-receptor antagonists.

Precautions: *General*– 1. Symptomatic response to nizatidine therapy does not preclude the presence of gastric malignancy.

2. Dosage should be reduced in patients with moderate to severe renal insufficiency.

3. In patients with normal renal function and uncomplicated hepatic dysfunction, the disposition of nizatidine is similar to that in normal subjects.

Laboratory Tests– False-positive tests for urobilinogen with Multistix® may occur during therapy.

Drug Interactions– No interactions have been observed with theophylline, chlordiazepoxide, lorazepam, lidocaine, phenytoin, and warfarin. Axid does not inhibit the cytochrome P-450 enzyme system; therefore, drug interactions mediated by inhibition of hepatic metabolism are not expected to occur. In patients given very high doses (3,900 mg) of aspirin daily, increased serum salicylate levels were seen when nizatidine, 150 mg b.i.d., was administered concurrently.

Carcinogenesis, Mutagenesis, Impairment of Fertility– A 2-year oral carcinogenicity study in rats with doses as high as 500 mg/kg/day (about 80 times the recommended daily therapeutic dose) showed no evidence of a carcinogenic effect. There was a dose-related increase in the density of enterochromaffin-like (ECL) cells in the gastric oxyntic mucosa. In a 2-year study in mice, there was no evidence of a carcinogenic effect in male mice, although hyperplastic nodules of the liver were increased in the high-dose males as compared with placebo. Female mice given the high dose of Axid (2,000 mg/kg/day, about 330 times the human dose) showed marginally statistically significant increases in hepatic carcinoma and hepatic nodular hyperplasia with no numerical increase seen in any of the other dose groups.The rate of hepatic carcinoma in the high-dose animals was within the historical control limits seen for the strain of mice used. The female mice were given a dose larger than the maximum tolerated dose, as indicated by excessive (30%) weight decrement as compared with concurrent controls and evidence of mild liver injury (transaminase elevations). The occurrence of a marginal finding at high dose only in animals given an excessive and somewhat hepatotoxic dose, with no evidence of a carcinogenic effect in rats, male mice, and female mice (given up to 360 mg/kg/day, about 60 times the human dose), and a negative mutagenicity battery are not considered evidence of a carcinogenic potential for Axid.

Axid was not mutagenic in a battery of tests performed to evaluate its potential genetic toxicity, including bacterial mutation tests, unscheduled DNA synthesis, sister chromatid exchange, mouse lymphoma assay, chromosome aberration tests, and a micronucleus test.

In a 2-generation, perinatal and postnatal fertility study in rats, doses of nizatidine up to 650 mg/kg/day produced no adverse effects on the reproductive performance of parental animals or their progeny.

Pregnancy – Teratogenic Effects – Pregnancy Category C – Oral reproduction studies in rats at doses up to 300 times the human dose and in Dutch Belted rabbits at doses up to 55 times the human dose revealed no evidence of impaired fertility or teratogenic effect; but, at a dose equivalent to 300 times the human dose, treated rabbits had abortions, decreased number of live fetuses, and depressed fetal weights. On intravenous administration to pregnant New Zealand White rabbits, nizatidine at 20 mg/kg produced cardiac enlargement, coarctation of the aortic arch, and cutaneous edema in 1 fetus, and at 50 mg/kg, it produced ventricular anomaly, distended abdomen, spina bifida, hydrocephaly, and enlarged heart in 1 fetus. There are, however, no adequate and well-controlled studies in pregnant women. It is also not known whether nizatidine can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. Nizatidine should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nursing Mothers– Studies in lactating women have shown that 0.1% of an oral dose is secreted in human milk in proportion to plasma concentrations. Because of growth depression in pups reared by treated lactating rats, a decision should be made whether to discontinue nursing or the drug, taking into account the importance of the drug to the mother.

Pediatric Use– Safety and effectiveness in children have not been established.

Use in Elderly Patients– Healing rates in elderly patients were similar to those in younger age groups as were the rates of adverse events and laboratory test abnormalities. Age alone may not be an important factor in the disposition of nizatidine. Elderly patients may have reduced renal function.

Adverse Reactions: Worldwide, controlled clinical trials included over 6,000 patients given nizatidine in studies of varying durations. Placebo-controlled trials in the United States and Canada included over 2,600 patients given nizatidine and over 1,700 given placebo. Among the adverse events in these placebo-controlled trials, only anemia (0.2% vs 0%) and urticaria (0.5% vs 0.1%) were significantly more common in the nizatidine group. Of the adverse events that occurred at a frequency of 1% or more, there was no statistically significant difference between Axid and placebo in the incidence of any of these events (see package insert for complete information).

A variety of less common events were also reported; it was not possible to determine whether these were caused by nizatidine.

Hepatic– Hepatocellular injury (elevated liver enzyme tests or alkaline phosphatase) possibly or probably related to nizatidine occurred in some patients. In some cases, there was marked elevation (>500 IU/L) in SGOT or SGPT and, in a single instance, SGPT was >2,000 IU/L. The incidence of elevated liver enzymes overall and elevations of up to 3 times the upper limit of normal, however, did not significantly differ from that in placebo patients. All abnormalities were reversible after discontinuation of Axid. Since market introduction, hepatitis and jaundice have been reported. Rare cases of cholestatic or mixed hepatocellular and cholestatic injury with jaundice have been reported with reversal of the abnormalities after discontinuation of Axid.

Cardiovascular– In clinical pharmacology studies, short episodes of asymptomatic ventricular tachycardia occurred in 2 individuals administered Axid and in 3 untreated subjects.

CNS– Rare cases of reversible mental confusion have been reported.

Endocrine– Clinical pharmacology studies and controlled clinical trials showed no evidence of anti-androgenic activity due to nizatidine. Impotence and decreased libido were reported with similar frequency by patients on nizatidine and those on placebo. Gynecomastia has been reported rarely.

Hematologic– Anemia was reported significantly more frequently in nizatidine than in placebo-treated patients. Fatal thrombocytopenia was reported in a patient treated with nizatidine and another H_2-receptor antagonist. This patient had previously experienced thrombocytopenia while taking other drugs. Rare cases of thrombocytopenic purpura have been reported.

Integumental– Urticaria was reported significantly more frequently in nizatidine- than in placebo-treated patients. Rash and exfoliative dermatitis were also reported.

Hypersensitivity– As with other H_2-receptor antagonists, rare cases of anaphylaxis following nizatidine administration have been reported. Rare episodes of hypersensitivity reactions (eg, bronchospasm, laryngeal edema, rash, and eosinophilia) have been reported.

Other– Hyperuricemia unassociated with gout or nephrolithiasis was reported. Eosinophilia, fever, and nausea related to nizatidine have been reported.

Overdosage: Overdoses of Axid have been reported rarely. If overdosage occurs, activated charcoal, emesis, or lavage should be considered along with clinical monitoring and supportive therapy. The ability of hemodialysis to remove nizatidine from the body has not been conclusively demonstrated, however, due to its large volume of distribution, nizatidine is not expected to be efficiently removed from the body by this method.

PV 2093 AMP [101591]

Additional information available to the profession on request

Lilly

Eli Lilly and Company
Indianapolis, Indiana
46285

NZ-2947-B-249304

© 1991, ELI LILLY AND COMPANY

Rx C3: Coughs, Colds, Flu . . .

S-T FORTE™

SUGAR FREE

NDC #0372-0005-16

Hydrocodone Bitartrate 2.50 mg./5 ml.; (Warning: May be habit forming.) Phenylephrine & Phenylpropanolamine Hcl. āā 5 mg./5 ml.; Pheniramine Maleate 13.33 mg./5 ml.; Guiafenesin 80 mg./5 ml. & 5% Alcohol by volume.

Rx C3—Same formula with sugar.

S-T Forte Syrup NDC #0372-0004-16

Complete information in the package.

(401) 942-8555

Toll Free 1-800-638-SCOT

TM: **Scot-Tussin Pharmacal Co., Inc.**
Cranston, R.I. 02920-0217

Rhode Island

MD NEEDED

for private walk-in primary care facility. Up-to-date equipment. Full staff of professionals.

Must be experienced in minor surgery and orthopedics.

30-40 hours per week. Malpractice insurance. Vacation. Position available early 1992.

Please send resume to:

Box M
RHODE ISLAND MEDICINE
106 Francis Street
Providence, RI 02903

Pre-operative Medical Evaluation: Minimizing Perioperative Risk

Fred Rotenberg, MD
Carl Schwartz, MD

Some 50,000 Americans have perioperative myocardial infarctions each year.

Problems with airway management have historically led the list of causes of anesthesia-related morbidity and mortality. With the advent of continuous monitoring of oxygenation and ventilation in the perioperative period, such airway problems as esophageal intubation, hypoxic arrest, encephalopathy, etc. have become extremely rare. Pulse oximetry and end tidal capnography are now standards of care for patients undergoing general anesthesia. When combined with sophisticated anesthesia machine disconnect alarms, apnea monitors, inspired oxygen monitors, and continuous electrocardiographic monitors, the risk of anesthesia has been greatly reduced. Despite these technological advances, the vigilance and expertise of the anesthesiologist remain the prime determinant of safe anesthetic practice.

Anesthesiologists now face new challenges anesthetizing the "high risk" patient. Cardiovascular and pulmonary complications are the major risks this group of patients face. Some 50,000 Americans have perioperative myocardial infarctions (MI) each year. More than half of the 40,000 postoperative deaths annually are caused by cardiac events.

In this article, we will try to identify these high risk patients, address ways of optimizing their preoperative status, and consider anesthetic plans which will minimize the risk. Given our limited space, our goal is to provide an overview of this broad topic for our medical and surgical colleagues. Recent reviews of these topics are available for more detail.[1,2]

Fred Rotenberg, MD, is Co-Director of Cardiac Anesthesia and Assistant Anesthetist at Rhode Island Hospital and Clinical Assistant Professor of Surgery at Brown University, Providence, Rhode Island.

Carl Schwartz, MD, is Assistant Anesthetist at Rhode Island Hospital and Clinical Assistant Professor of Surgery at Brown University, Providence, Rhode Island.

Cardiovascular Morbidity

Perioperative cardiac morbidity (including myocardial infarction, unstable angina, congestive heart failure or serious arrhythmia) is the leading cause of death following surgery. Mortality following perioperative MI remains extremely high (40-70%).[4,7]

Table 1 presents generally accepted rates of postoperative MI. When postoperative MI occurs, it is commonly (50-70%) silent (ie, without classic symptomatology) compared to 20-40% of the time in nonsurgical patients. In addition, postoperative MIs most often occur at least 48 hours after surgery. Postoperative MIs, therefore, may go undetected.

It is, nevertheless, possible to reduce the incidence of perioperative MI in certain patient populations. Clearly those patients with recent myocardial infarction (within 3 months) have a higher incidence of perioperative reinfarction than do those patients without previous infarction or in those whose infarct is greater than six months old.[7,25,26] It is common practice to delay elective surgery until at least six months following MI, yet no data exist that confirms that such practice reduces risk.

Patients with significant coronary artery disease (CAD) who are scheduled for major vascular surgery ben-

ABBREVIATIONS USED:
AS: aortic stenosis
ASA: American Society of Anesthesiologists
ATN: acute tubular necrosis
BUN: blood urea nitrogen
CABG: coronary artery bypass grafting
CAD: coronary artery disease
CHF: congestive heart failure
CT: computerized tomography
FENa: fractional excretion of sodium
FEV: forced respiratory volume
FVC: forced vital capacity
GFR: glomerular filtration rate
MI: myocardial infarction
MVV: maximal voluntary ventilation

efit from coronary artery bypass grafting (CABG) prior to their vascular surgery. Perioperative mortality following the vascular procedure is then reduced and five year survival data is markedly improved.[6] Table 2 summarizes this data. This benefit begins to be seen one month following CABG. In contrast, combined CABG and noncardiac surgery increases mortality by 4-13%.[3] No data is available as to whether or not percutaneous transluminal coronary angioplasty provides similar protection.

Anesthetic management may also reduce the risk of perioperative cardiac morbidity. Rao, et al have suggested that outcome may be improved in high risk patients by providing intensive monitoring and aggressive medical treatment in the perioperative period.[7] Yeager, et al[8] claim that combined epidural and general anesthesia carries less risk of cardiac morbidity than general anesthesia alone.

Assessing a patient's risk for perioperative cardiac morbidity then becomes important. Expensive, potentially risky or experimental treatments would obviously not be offered to these high risk patients. In addition, efficacy of new treatments could only be judged in patients carrying similar risk.

Cardiac Risk Assessment

History

Predicting perioperative cardiac morbidity can be based on the patient's history, diagnostic tests, nature of the operation, anesthetic management and perioperative events.

An overall assessment of anesthetic risk may be made preoperatively based on the Dripps (or American Society of Anesthesiologists) classification of "physical status" (Table 3).[5] This classification, based on the patient's history, is somewhat subjective, but still provides good predictive value for perioperative death (Tables 4 and 5). Newer methods of risk stratification (eg, Goldman Multifactorial Cardiac Risk Index)[9] are more objective than the ASA classification but are probably no more sensitive or specific. There are studies which refute the predictive value of both of these indices.

Table 1. **Incidence of Myocardial Infarction Following Noncardiac Surgery**

General population following noncardiac surgery	<0.2%
Patients with CAD	1.1%
Patients older than 40 (with or without CAD)	1.8%
Patients undergoing vascular surgery	1-15%
Patients with previous MI (>6 month previously)	5-8%
Patients with previous MI (within previous 6 months)	6-40%

The only consistent historical predictors of cardiac morbidity are recent (ie, within previous three months) myocardial infarction and current heart failure (when defined by S3 and JVD). Previous heart failure and low ejection fraction are commonly correlated with perioperative cardiac morbidity in patients following major vascular surgery, as are diabetes, clinically significant aortic stenosis, and significant dysrrhythmias. Interestingly, hypertension, age, history of angina, peripheral vascular disease, and smoking have not been shown to be independent risk factors.[10]

The only consistent historical predictors of cardiac morbidity are recent myocardial infarction and current heart failure. . .

Although aortic stenosis increases the incidence of perioperative cardiac death fourteen fold,[9] such severe outcome is still rare. Recent data show uneventful surgery may be expected in 80% of patients with moderate to severe AS. The other 20% showed transient blood pressure changes. No deaths related to the valvular lesion occurred.[11]

Aortic regurgitation or mitral valve disease, when not associated with ventricular dysfunction, dysrrhythmia, pulmonary hypertension or CAD, do not carry undue risk of perioperative mortality. Postoperative pulmonary edema is more common, however, in patients with valvular disease.[12]

Diagnostic Tests

Electrocardiographic evidence of ischemic heart disease does not, in itself, predict perioperative cardiac morbidity. Indeed the EKG may be normal in 25-50% of patients with CAD. It is rarely normal in patients with significant left ventricular dysfunction.

Ambulatory EKG monitoring demonstrates good correlation between ST depression during normal activity, abnormal angiographic findings, and subsequent myocardial infarction. It is unclear whether these EKG abnormalities predict perioperative cardiac morbidity.[24]

Several studies report that a positive ischemic response and low exercise capacity during exercise tolerance testing predicts adverse outcome following noncardiac surgery. One study found it not to be predictive.[13]

Abnormal left ventricular function demonstrated by echocardiography or radioventriculogram studies may predict perioperative ventricular dys-

Table 2. **The Effect of Previous Coronary Artery Bypass Surgery on Incidence of Subsequent Cardiac Morbidity Following Major Noncardiac Surgery**

	Previous CABG	No Previous CABG
Post-op MI	0-1.2%	1.1-6%
Mortality	0.5-0.9%	1-2.4%

function. Low ejection fraction (<40%) only predicts perioperative cardiac morbidity in patients coming for vascular surgery. Specifically, patients having abdominal aortic resection or lower extremity revascularization and preoperative ejection fraction <35% have an associated 75-85% incidence of perioperative MI. Those with ejection fraction >35% have a 20% incidence. In nonvascular patients for abdominal or thoracic operation, ejection fraction was not a significant predictor.[14-16] Whether these studies are more helpful than a careful history and physical examination in predicting perioperative risk is unclear.

...a positive ischemic response and low exercise capacity during exercise tolerance testing predicts adverse outcome following noncardiac surgery.

Dipyridamole Thallium stress testing has been found to be highly sensitive, reasonably specific, and very accurate in identifying the absence of coronary disease in patients coming for vascular surgery. A recent study by Mangano, et al,[17] however, found that more than 50% of adverse outcomes or perioperative ischemia occurred in patients without redistribution defects. Even more disturbing is this test's low positive predictive value. In order to reduce the number of false positive results, only high risk patients (those with history of angina, previous MI, CHF or diabetes), should be studied.[18] The recent Mangano study[17] also found no association between redistribution defects and adverse cardiac outcomes or perioperative ischemia.

Cardiac catheterization should be considered for those patients with evidence of significant coronary artery disease. Catheterization documented CAD warrants consideration of coronary artery bypass grafting prior to major vascular surgery.

Operative Considerations

Emergency surgery, prolonged operation, intra-thoracic, or upper abdominal surgery no longer appear to be independent predictors of perioperative cardiac morbidity. When they are associated with perioperative hypotension, myocardial ischemia or left ventricular dysfunction, risk is definitely increased.

Table 3. **Dripps Criteria for Identifying High-Risk Patients on Basis of History**

Class I	There is no physiologic, biochemical, or psychiatric disturbance. The pathological process for which operation is to be performed is localized and not conducive to systemic disturbance. Examples: a fit patient with inguinal hernia or fibroid uterus in an otherwise healthy woman.
Class II	Mild to moderate systemic disturbance caused either by the condition to be treated surgically or by other pathophysiological processes. Examples: presence of mild diabetes, essential hypertension, or anemia.
Class III	Rather severe systemic disturbance or pathology from whatever cause, even though it may not be possible to define the degree of disability with finality. Examples: severe diabetes with vascular complication, moderate to severe degrees of pulmonary insufficiency, stable angina pectoris, or healed myocardial infarction.
Class IV	Indicative of the patient with a severe systemic disorder already life-threatening and not always correctable by the operative procedure. Examples: advanced degrees of cardiac, pulmonary, hepatic, renal or endocrine insufficiency.
Class V	This category embraces the moribund patient who has little chance of survival but is submitted to operation in desperation. Examples: the burst aneurysm with the patient in profound shock, major cerebral trauma with rapidly increasing intracranial pressure, or massive pulmonary embolus.
Emerg. Operation (E)	Any patient in one of the classes listed above who is operated upon as an emergency is considered to be in somewhat poorer physical condition. The letter E is placed beside the numerical classification.

Anesthetic Management

It is difficult to prove that the choice of anesthetic alters the risk of perioperative cardiac morbidity. Extremely large studies are needed to look at such uncommon occurrences. For example, to determine whether a change in practice may reduce perioperative mortality from 1% to 0.5%, approximately 7,400 patients would have to be studied assuming a type 1 error of 0.1 and the power of the test at 80%. Such large studies are very rare.

Some studies do show that choosing a regional anesthetic can reduce risk in certain high risk patients. Spinal anesthesia for transurethral prostate resection in patients with previous myocardial infarction is associated with a reinfarction rate of less than 1% compared with a 2-8% rate under general anesthesia. Also in patients with a history of heart failure, spinal anesthesia neither introduces nor worsens heart failure, whereas general anesthesia is associated with higher rates of both.[8,12]

Similarly it is difficult to prove that the choice of anesthesiologist alters the risk of perioperative cardiac morbidity. Although it is universally accepted that the anesthesiologists' skill is a major determinant of outcome, few studies have directly addressed this issue. Patients anesthetized for

open heart surgery by subspecialty trained cardiac anesthesiologist (who routinely anesthetize such patients) seem to have less morbidity than those patients anesthetized by less experienced practitioners.[20]

Do intraoperative events affect outcome? Intraoperative hypotension is an important predictor of perioperative cardiac morbidity, whereas hypertension or tachycardia are not predictive. Data from Rao, et al[7] also suggest that aggressive hemodynamic management in the intraoperative and postoperative period may improve outcome.

Perioperative Myocardial Ischemia

Does perioperative myocardial ischemia lead to postoperative myocardial infarction? Slogoff and Keats certainly confirmed such a correlation in patients coming for coronary artery bypass grafting.[20,21] During non-cardiac surgery it is unclear whether ST changes predict perioperative myocardial infarction. Preliminary data suggest that intraoperative wall motion abnormalities noted on transesophageal echocardiography do predict perioperative cardiac morbidity.[22]

A recent study suggests that postoperative myocardial ischemia is a more sensitive predictor of adverse cardiac outcomes than other markers. Unfortunately, such ischemia is often silent. In high risk patients with electrocardiographically documented postoperative ischemia, there was a 2.8 fold increased risk of all adverse outcomes and a 9.2 fold increased risk of cardiac death, MI or unstable angina. More importantly, no other clinical, historical or perioperative variable, (including cardiac risk index, history of previous MI or CHF of intraoperative myocardial ischemia) was associated with ischemic events.[23]

Using postoperative events as predictors of poor outcome does not help the practitioner trying to reduce perioperative risk (unless intervening at this stage would then alter outcome). Again, the literature does not directly address this issue. The study by Rao, et al, however, suggests that aggressive management of hemodynamics throughout the perioperative period reduces perioperative cardiac morbidity.[7]

Table 4. **Mortality Rates by Age and Physical Status Category for all Patients at Massachusetts General Hospital, 1973-1976**

Physical Status	Age			
	0-34	35-64	65+	All Ages
1,2	0.1%	0.3%	1.0%	0.3%
3	5.0%	3.9%	5.2%	4.6%
4	27.5%	21.4%	31.0%	25.9%
5	70.2%	71.3%	75.8%	72.4%
All	1.0%	2.6%	5.8%	2.6%

From R Hirsh, et al (eds.): Health Care Delivery in Anesthesia, Philadelphia, GF Stickley, 1979. p. 100.

Pulmonary Disease

Postoperative pulmonary complications rank second behind cardiovascular complications as a cause of perioperative mortality. Patients with significant chronic lung disease are at greater risk of postoperative respiratory failure than the general population. They have less pulmonary reserve to compensate for the hypoventilation and hypoxemia superimposed by anesthesia and surgery. The postoperative mortality rate for patients with moderate to severe chronic lung disease following general anesthesia is approximately 7%. Upper abdominal and thoracic surgery carry a mortality rate double that of other procedures.

A patient's pulmonary function is evaluated preoperatively to assess the risk associated with the surgical procedure and to optimize perioperative management. Hopefully, by implementing a therapeutic plan based on the data obtained in our preoperative evaluation, we can modify that risk and improve outcome. The most reliable and cost-effective means of evaluating pulmonary risk is by spirometry and arterial blood gas analysis in conjunction with a history and physical examination.[28-30]

The most reliable and cost-effective means of evaluating pulmonary risk is by spirometry and arterial blood gas analysis in conjunction with a history and physical examination.

Preoperative arterial blood gas analysis helps quantify the severity of pulmonary dysfunction. Patients with severe hypoxemia (PaO_2<60mm Hg breathing room air) or CO_2 retention ($PaCO_2$>50mm Hg) are at increased risk for postoperative pulmonary complications.

Table 5. **Mortality Rates for Each ASAPhysical Status Classification**

Physical Status	Anesthetics	Death	Mortality %
I	50,703	43	0.08
II	12,601	34	0.27
III	3,626	66	1.8
IV	850	66	7.8
V	608	57	9.4

From CJ Vacanti, RJ VanHouten, RC Hill. A statistical analysis of the relationship of physical status to postoperative mortality in 68,388 cases. Anesth Analg 49:233, 1978.

Spirometric flow volume loops can localize physiological obstruction to air flow. Differentiating variable extrathoracic from variable intrathoracic and from fixed airway obstructions, permits rational anesthetic and surgical plans. Timed spirometric tests identify and quantify obstructive and/or restrictive lung disease. The forced vital capacity (FVC), forced expiratory volume in one second (FEV_1), FEV_1/FVC, maximum mid-expiratory flow rate, forced expiratory flows at 25-75% of vital capacity (FEF_{25-75}), peak expiratory flow rate and maximal voluntary ventilation (MVV) are included in this battery of tests.

Although it is difficult to assign spirometric values that clearly define respiratory risk, the values noted in Table 6 are commonly accepted as minimal values below which the risk of postoperative pulmonary complications are increased.

It is useful to repeat these tests after a therapeutic challenge with bronchodilators to determine if there is improvement. Preoperative institution of a therapeutic regimen including chest physiotherapy, bronchodilators, corticosteroids, antibiotics for two to three days and discontinuance of smoking may improve pulmonary status. Assessment of the ability of aerosolized atropine to attenuate bronchospasm may be particularly important to the anesthesiologist, since this therapy may attenuate bronchospastic responses to foreign bodies, including the response to endotracheal intubation in those patients prone to bronchospasm. A bronchospastic patient should be free of wheezing before undergoing elective surgery.

It is well known that upper abdominal and thoracic operations have the greatest negative effect on pulmonary function. Thus the patient undergoing upper abdominal surgery who does not achieve these values noted in Table 6 are at increased risk for postoperative ventilatory failure. Aggressive treatment with bronchodilators and pulmonary toilet starting preoperatively is warranted. In addition, since 80% of pulmonary function is usually recovered by the third postoperative day, support with mechanical ventilation may be needed for two to three days postoperatively.

Criteria for acceptable pulmonary function tests are stricter in lung surgery than other surgical procedures. Lung resection certainly causes more direct trauma to the respiratory system and reduces surface area for gas exchange. Since preoperative evaluation of lung cancer is imprecise, all patients for lung resection should be evaluated as if a pneumonectomy is to be performed. It then becomes necessary to estimate the remaining lung function after pneumonectomy. This is done by performing split function lung studies, including the lateral position test, perfusion scanning, ventilation-perfusion scanning and unilateral pulmonary artery occlusion. After performing the split function lung studies, predicted postoperative FEV, and vital capacity can be calculated. Predicted postoperative FEV_1 less than one liter or forced vital capacity less than 20cc/Kg historically has defined inoperable disease.

Table 6. Spirometric Values Indicating Increased Perioperative Pulmonary Risk

FVC <50% predicted
FEV_1 <50% predicted or <2L
FEV_1/FVC <50%
MVV <50% predicted or <50L/min
FEF_{25-75} <50% predicted

Cerebrovascular Disease

Although perioperative stroke is rare, the risk of cerebral ischemia is of particular concern in patients with previous stroke, transient ischemic attacks, or carotid bruits. These patients should be thoroughly evaluated preoperatively with studies assessing cerebral blood flow.[31-32]

Patients with carotid bruits should be asked detailed questions about symptoms which might be due to cerebral ischemia. Asymptomatic carotid bruits are found in about 7% of the population over the age of 65, and the frequency increases with further aging.[33] Multiple studies have failed to show an increased risk of perioperative stroke in patients with asymptomatic bruits.[34,35]

Conversely, patients with asymptomatic bruits coming for open heart surgery may have increased risk of perioperative stroke. Two studies demonstrate increased risk although another study failed to show added risk of stroke.[38] Furthermore, prophylactic carotid endarterectomy before CABG did not decrease the perioperative stroke rate of 3-6%. These studies argue against further evaluation of asymptomatic carotid bruits or prophylactic carotid endarterectomy.[32]

Asymptomatic carotid bruits remain useful as a marker for systemic atherosclerosis and coronary artery disease. Long-term studies by Evans and Cooperman and by Chambers and Norris indicate that patients with asymptomatic carotid bruits are more likely to have an ischemic cardiac event than a stroke.[35,39]

Patients with symptomatic carotid bruits have a two-to-three times greater risk of stroke.[31] The risk of stroke from cerebral angiogram and carotid endarterectomy is 1-2% lower than the yearly frequency of spontaneous stroke in symptomatic patients. This should justify the benefits of diagnostic testing for carotid disease and prophylactic carotid endarterectomy in these patients.[32]

For acute stroke patients, the history, physical examination and a CT scan provide most of the information needed to evaluate these patients. The CT scan differentiates ischemic infarction from hemorrhage and can help evaluate the presence of elevated intracranial pressure and the need for emergent surgical intervention.

Cerebrovascular instability is common in the acute stroke patient. Vasomotor responses do not normalize until about four to six weeks after acute stroke.[40] Within this period, the perioperative risk of inducing another stroke remains significantly elevated and thus elective surgery should be delayed.[41]

Renal Disease

The major problem encountered in evaluating renal dysfunction is that it is usually asymptomatic until uremia occurs. Postoperative renal failure has a mortality rate exceeding 50% despite aggressive treatment and this mortality rate increases significantly as other organ systems fail. One of the major risk factors for developing postoperative renal failure is preexisting renal dysfunction.[32,42] Perioperative renal dysfunction also affects fluid and electrolyte balance and the pharmacokinetics and pharmacodynamics of various drugs.

When surgery must be performed emergently in the renally compromised patient, measures for prevention of further renal insults should be undertaken.

Serum creatinine and BUN are commonly used tests of renal function. Usually for every doubling of serum creatinine, GFR is decreased by half. Since BUN concentration can fluctuate due to changes in dietary intake and metabolism, it might not reflect renal function accurately. Creatinine clearance helps quantify the extent of renal dysfunction.

In acute oliguric renal dysfunction, urinary indexes can help distinguish a pre-renal state from intrinsic renal failure (eg, acute tubular necrosis). A fractional excretion of sodium (FENa) less than 1% implies the presence of pre-renal azotemia, whereas a value greater than 1% indicates ATN.[43]

Pre-renal azotemia often responds to careful preoperative hydration. If FENa is greater than 1%, possible causes of ATN should be investigated. The prior use of therapeutic interventions to increase urine output, such as fluid challenges, diuretics or renal dose dopamine will affect urinary indexes, making interpretation difficult.[32]

Once the underlying cause of renal dysfunction has been identified and treated, renal function should be allowed to stabilize for several days before anesthesia and surgery are attempted. When surgery must be performed emergently in the renally compromised patient, measures for prevention of further renal insults should be undertaken. These include loop diuretics, mannitol and low-dose dopamine, in an effort to maintain urine output and preserve remaining renal function.

Acknowledgments

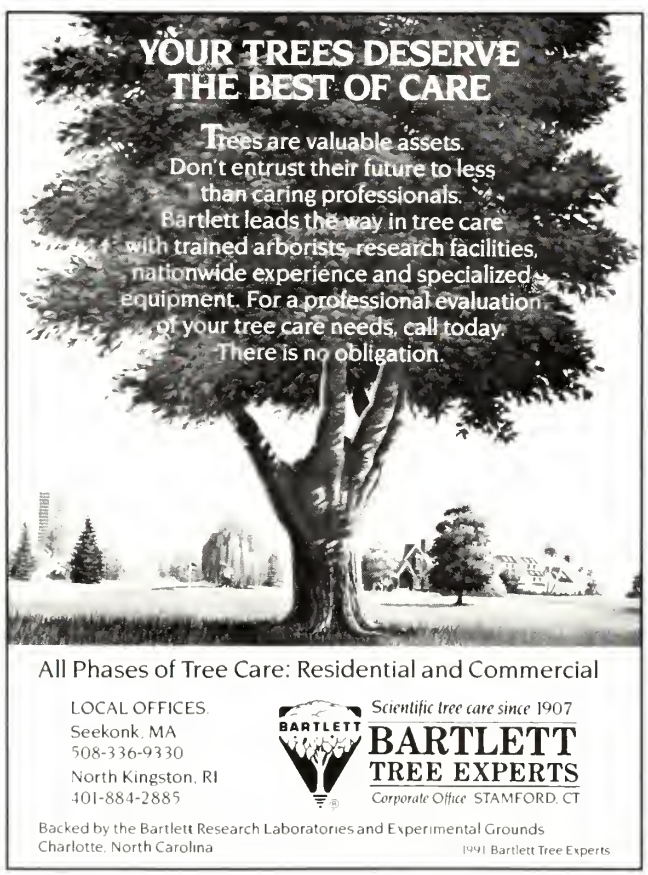
The authors gratefully acknowledge the expert secretarial work of Christine Abatiello.

References

1. Mangano DT. Perioperative cardiac morbidity. Anesthesiology 71(1):153-184, 1990.
2. Brown DL. Risk and outcome in anesthesia. Philadelphia, JB Lippincott, 1988.
3. Crawford ES, Morris CG, Howell JF, et al. Operative risk in patients with previous coronary artery bypass. Ann Thorac Surg 26:215, 1974.
4. Goldman L. Multifactorial index of cardiac risk in noncardiac surgery: ten year status report. J Cardiothoracic Anes 1:237, 1987.
5. Dripps RD, Lamont A, Eckenhoff JE. The role of anesthesia in surgical mortality. JAMA 178:261-266, 1961.
6. Herzer NR, Bevan EG, Young JR, et al. Coronary artery disease in peripheral vascular patients: A classification of 1000 coronary angiograms and results of surgical management. Ann Surg 199:223, 1984.
7. Rao TLK, Jacobs KH, El-Etr AA. Reinfarction following anesthesia in patients with myocardial infarction. Anesthesiology 59:499, 1983.
8. Yeager M, Glass D, Neff R, et al. Epidural anesthesia and analgesia in high risk surgical patients. Anesthesiology 66:729-735, 1987.
9. Goldman L, Caldera DL, Nussbaum SR, et al. Multifactorial index of cardiac risk in noncardiac surgical procedures. NEJM 297:845-850, 1977.
10. Mangano DT. Assessment of risk for cardiac and noncardiac surgical procedures. Anesthesiology Clinics of North America 9(3):521-551, September 1991.
11. Wong KC, Schultz JR, Jr. Preoperative hypokalemia and the cardiac patient. In Stanley TH, Sperry RJ (eds.): Anesthesiology and the Heart. Norwell, MA. Kluwer Academic, 1990, pp 111-18.
12. Goldman L, Caldera DL, Southwick FS, et al. Cardiac risk factors and complications in noncardiac surgery. Medicine 57:357-370, 1978.
13. Carliner NH, Fisher ML, Plotnick GD, et al. Routine perioperative exercise testing in patients undergoing major noncardiac surgery. Am J Cardiology 56:51-57, 1985.
14. Pasternack PF, Imparato AM, Bear G, et al. The value of radionuclide angiography as a predictor of perioperative myocardial infarction in patients undergoing abdominal aortic aneurysm resection. J Vasc Surg 1:320-325, 1984.
15. Pastenrack PF, Imparato AM, Riles TS, et al. The value of radionuclide angiography as a prediction of perioperative myocardial infarction in patients undergoing lower extremity revascularization procedures. Circulation 72 (Suppl II):II-13 - II-17, 1985.
16. Gerson MC, Hurst JM, Hertzberg VS, et al. Cardiac prognosis in noncardiac geriatric surgery. Ann Intern Med 103:832-837, 1985.
17. Mangano DT, London MJ, Tubay JF, et al. Dipyridamole thallium-201 scintigraphy as a preoperative screening test. A reexamination of its predictive potential. Circulation 84:493-502, 1991.
18. Eagle KA, Coley CM, Newell JB, et al. Combining clinical and thallium data optimizes preoperative assessment of cardiac risk before major vascular surgery. Ann Intern Med 110:859-866, 1989.
20. Slogoff S, Keats A. Does perioperative myocardial ischemia lead to postoperative myocardial infarction? Anesthesiology 62:107-114, 1985.
21. Slogoff S, Keats A. Further observations on perioperative myocardial ischemia. Anesthesiology 65:538-542, 1986.
22. Smith JS, Cahalan MK, Benefiel DJ, et al. Intraoperative detection of myocardial ischemia in high-risk patients: Electrocardiography versus two-dimensional transesophageal echocardiography. Circulation 72:1015-1021, 1985.
23. Mangano D, Browner WS, Hollenberg M, et al. Association of perioperative myocardial ischemia with cardiac morbidity and mortality in men undergoing noncardiac surgery. NEJM 323:1781-1788 1990.
24. Fleisher LA, Rosenbaum SH, Nelson AH, Barash PG. The predictive value of preoperative silent ischemia for postoperative ischemic cardiac events in vascular and nonvascular surgery patients. Am Heart J 122:980-986, 1991.
25. Tarhan S, Moffitt AE, Taylor WR, Giuliani ER. Myocardial infarction after general anesthesia. JAMA 220:1451-1454, 1972.
26. Steen PA, Tinker JH, Tarhan S. Myocardial reinfarction after anesthesia and surgery. JAMA 239:2566-2570, 1978.
27. Vacanti CJ, VanHouten RJ, Hill RI. A statistical analysis of the relationship of physical status to postoperative mortality in 68,388 cases. Anes Analg 49:565-566, 1970.
28. Tisi GM. Preoperative evaluation of pul-

monary function: Validity, indications and benefits. Am Rev Respir Dis 119:293-307, 1979.
[29] Boysen PG. Evaluation of pulmonary risk. In: Refresher Courses in Anesthesiology, Vol. 17. The American Society of Anesthesiologists. Philadelphia, JP Lippincott Co, 1989. pp. 17-27.
[30] Boysen PG. Pulmonary disease and perioperative risk, Risk and Outcome in Anesthesia. Edited by Brown DL. Philadelphia JB Lippincott, 1988. pp. 50-73.
[31] American-Canadian Cooperative Study Group. Persantine aspirin trial in cerebral ischemia II: Endpoint results. Stroke 1985:406-415.
[32] Cheng EY, Wang-Cheng RM. Impact of aging on preoperative evaluation. Journal of Clinical Anesthesia 3:324-343, 1991.
[33] Van Ruiswyk J, et al. The natural history of carotid bruits in elderly persons. Ann Int Med 112:340-343, 1990.
[34] Wolf PA, et al. Asymptomatic carotid bruit and risk of stroke. The Framingham Study. JAMA 245:1442-1445, 1981.
[35] Chambers BR, Norris JW. Outcome in patients with asymptomatic neck bruits. N Eng J Med 315:860-865, 1987.
[36] Mehigan JT, et al. A planned approach to coexistent cerebrovascular disease in coronary artery bypass candidates. Arch Surg 112:1403-1409, 1977.
[37] Hertzner NR, et al. Staged and combined surgical approach to simultaneous carotid and coronary vascular disease. Surgery 84:803-811, 1978.
[38] Fulran AJ, Cracium AE. Risk of stroke during coronary artery bypass graft surgery in patients with internal carotid artery disease documented by angiography. Stroke 16:797-799, 1985.
[39] Evans WE, Cooperman M. The significance of asymptomatic bruits in preoperative patients. Surgery 83:521-522, 1978.
[40] Paulson PB. Cerebral apoplexy (stroke): pathogenesis, pathophysiology, and therapy as illustrated by regional blood flow measurements in the brain. Stroke 2:327-360, 1971.
[41] Shapiro HM. Anesthesia effects upon cerebral blood flow, cerebral metabolism, EEG and evoked potentials. In: Miller RD (ed.) Anesthesia, 2nd ed. New York, Churchill Livingstone, 1249-1288, 1986.
[42] Sladen R. Effect of anesthesia and surgery on renal function. Crit Care Clin 3:373-393, 1987.
[43] Espinel CH, Gregory AW. Differential diagnosis of acute renal failure. Clin Nephrol 13:73-77, 1980.

Address correspondence to:
Fred Rotenberg, MD
Department of Anesthesiology
Rhode Island Hospital
593 Eddy Street
Providence, Rhode Island 02903


YOUR TREES DESERVE THE BEST OF CARE
Trees are valuable assets. Don't entrust their future to less than caring professionals. Bartlett leads the way in tree care with trained arborists, research facilities, nationwide experience and specialized equipment. For a professional evaluation of your tree care needs, call today. There is no obligation.
All Phases of Tree Care: Residential and Commercial
LOCAL OFFICES:
Seekonk, MA
508-336-9330
North Kingston, RI
401-884-2885
BARTLETT
Scientific tree care since 1907
BARTLETT TREE EXPERTS
Corporate Office STAMFORD, CT
Backed by the Bartlett Research Laboratories and Experimental Grounds
Charlotte, North Carolina
1991 Bartlett Tree Experts

STUART
PHARMACEUTICALS

SALUTES

RHODE ISLAND
ANESTHESIOLOGISTS

Perioperative Right Ventricular Failure

Arthur A. Bert, MD

Anesthesiologists...must be aware of the importance of right ventricular function in maintaining overall myocardial performance.

The role of the right ventricle (RV) in maintaining adequate cardiac output is currently undergoing an unprecedented period of interest. The relative neglect of the right ventricle in clinical cardiovascular research has been promoted by a number of considerations. First, early investigators like Starr et al,[1] who destroyed the canine RV free wall by cautery and found little change in systemic arterial or central venous pressure, concluded that the RV appeared to act merely as a passive conduit for blood moving to the left side of the heart. Secondly, clinical methods of assessing RV function have been hampered by its unique anatomy and only recently has bedside on-line monitoring become available. New investigations have identified RV dysfunction in a variety of disease states afflicting surgical patients. Anesthesiologists, surgeons and other clinicians caring for these patients must be aware of the importance of RV function in maintaining overall myocardial performance.

Anatomy of the Right Ventricle

The study of the RV is complicated by its distinctive anatomy and pattern of contraction. Unlike the left ventricle (LV), whose ellipsoidal shape is easily modelled, the RV is a crescent-shaped chamber with a thin and highly compliant free wall. Its chamber geometry is variable because of the structural influences and interactions with the pericardium, LV, and most importantly its shared wall, the interventricular septum. The RV cavity is anatomically and functionally divided into a posterior-inferior sinus (inflow) and an anterior-superior conus (outflow) region. These regions are embryologically and functionally distinct from each other. The sinus region extends from the tricuspid valve and includes the heavily trabeculated portion of the ventricle. The conus portion is separated from the sinus by the crista superaventricularis, extends to the pulmonic valve and is characterized by the presence of smooth circumvascular muscle bundles.

Blood supply to the RV flows primarily from the right coronary artery (RCA). The RCA courses inferiorly and posteriorly in the right atrioventricular groove, its branches supplying blood to the right atrium and the majority of the RV. In 80 to 85% of patients, the RCA supplies the posterior third of the septum and posterior LV via the posterior descending artery ("right dominant" system). Several unique features of RV coronary blood flow may account for the relative paucity of right ventricular infarctions seen clinically. First, unlike the LV which receives its coronary blood flow predominantly during diastole, the lower pressures present in the pulmonary circulation permit a lower RV wall tension during systole, well below arterial systolic pressure. As a result, a large pressure gradient or coronary perfusion of RV tissue exists throughout the cardiac cycle. Secondly the RV develops an extensive collateral circulation when obstructive stenoses are present in the RCA. The moderator band artery, a branch of the left anterior descending coronary artery, is a major source of blood supply to the anterior portion of the RV. In a series

Arthur A. Bert, MD, is Co-Director of Cardiothoracic Anesthesia and Assistant Anesthesiologist at Rhode Island Hospital and Assistant Clinical Professor of Surgery, Brown University, Providence, Rhode Island.

ABBREVIATIONS USED:
CABG: coronary artery bypass grafting
CPB: cardiopulmonary bypass
CVP: central venous pressure
ECG: electrocardiogram
IVS: interventricular septal defect
PAP: pulmonary artery pressure
PCWP: pulmonary capillary wedge pressure
PVR: pulmonary vascular resistance
PGE: prostaglandin E
RCA: right coronary artery
RV: right ventricle
RVEDP: right ventricular end-diastolic pressure
RVEDV: right ventricular end-diastolic volume
RVEF: right ventricular ejection fraction
L: left (as used in any of the above abbreviations)

of patients with proximal RCA occlusions, the degree of obstruction in collateral vessels from the left coronary artery, especially the moderator band artery, showed significant correlation with RV infarct size.[2]

Physiology of the Right Ventricle

The RV is physiologically more complex than the LV which has a relatively simplified mechanism of contraction. Right ventricular contraction proceeds sequentially from the sinus to the conus with the inflow tract contracting about 50 ms. prior to the outflow tract under normal physiologic conditions.[3] During contraction of the sinus, the conus dilates concomitantly with the initial expansion of the pulmonary artery. The conus remains contracted well into diastole. Right ventricular ejection continues during the relaxation phase of the inflow tract and RV free wall. Since ejection of blood continues after peak pressure is developed within the RV, the shape of RV pressure-volume loops differs greatly from those derived from the LV, are more triangular in shape, and make end-systole difficult to define.[4] In comparison to the LV, the velocity of right ventricular ejection increases more gradually, peaks later, and decreases more slowly.

The physiology of the RV is dominated by three salient mechanisms: 1) limited preload recruitability, 2) exquisite afterload dependence, and 3) ventricular interdependence. The diastolic compliance of the RV is high. The normal RV is more compliant than the left, not because of any intrinsic difference in the myocardium, but because its thinner walls are readily distensible. In the nonbeating normal dog heart, when the left and right ventricles are filled simultaneously to a pressure of 10 mmHg, the volume of the RV is about 35% greater than that of the left,[5] and the upper limit of normal for right ventricular end-diastolic pressure (RVEDP) in man is about one-half (6 mmHg) that of the LV (12 mmHg). RVEDP remains relatively low until dilation of the ventricle is limited by the pericardium.[6] Therefore the RV response to outflow impedance is predominantly ventricular dilation rather than increasing end-diastolic pressure. For example, Hurford et al[7] embolized the pulmonary vasculature with glass beads in dogs, increasing mean pulmonary artery pressure (PAP) from 14 to 48 mmHg. The right ventricular end-diastolic volume (RVEDV) increased from 91 to 131 ml, while RVEDP only increased from 4 to 8 mmHg. Preload augmentation will be efficacious in increasing RV output until RV dilation results in excessive myocardial fiber stretch.

Right ventricular function is exquisitely sensitive to changes in afterload.

Right ventricular function is exquisitely sensitive to changes in afterload. When considering an intact heart, afterload is nearly impossible to define precisely but most investigators believe it correlates well with the ventricular wall tension developed during systole. Clinically, a measure of outflow resistance is used, in the case of the RV, pulmonary vascular resistance (PVR) or mean PAP. If RV diastolic filling is maintained as RV afterload increases, right ventricular ejection fraction (RVEF) decreases and both end-diastolic volume and intracavitary pressures increase. This reflects the limited reserve of the thin-walled RV to increase contractility to compensate for acute increases in afterload. With chronic excessive afterload, RV hypertrophy develops, resulting in augmented contractility of the RV. Right ventricular output decreases linearly with any substantial increase in afterload, while in comparison the left ventricle maintains a nearly constant output over a wide range of afterload.[8] Thus an inverse relationship exists between RV afterload and RV stroke volume or RVEF. In the canine pulmonary microembolism study previously cited, mean PAP was progressively increased from 14 to 48 mmHg and resulted in RVEF decreasing from 39% to 18%.

While the sparse muscular power of the RV free wall remains the primary mechanism, several other factors limit RV compensatory responses to acute pulmonary artery hypertension. Right ventricular ischemia may further limit RV contractility. Blood flow to RV myocardium is propelled by the difference between aortic and RV tissue pressure, which is reasonably estimated by measuring intracavitary pressure. In the setting of acutely increased PVR, RV pressures increase, and RV myocardial blood flow must increase by coronary vasodilation to match the increased RV stroke work and oxygen consumption. Despite progressive increases in RVEDV with increasing pulmonary hypertension, Hurford's dogs did not exhibit evidence of RV free wall ischemia since RV myocardial blood flow increased by 150% with normal fatty acid extraction. However, RV free wall ischemia can occur during severe pulmonary hypertension in experimental animals with abnormal coronary anatomy, particularly when associated with systemic hypotension. Calvin[9] assessed oxygen supply/demand balance in the canine RV free wall during pulmonary hypertension. Doubling or tripling mean PAP did not induce RV ischemia despite decreasing cardiac output since systemic blood pressure was maintained. Further embolization which decreased cardiac output by 30% and mean aortic pressure by over 50%, caused free wall ischemia. Initially, as RV free wall oxygen requirements increased from pressure overload and dilation, coronary blood flow increased proportionately without causing ischemia. But further increases in RV afterload eventually caused regional oxygen demand to outstrip supply, resulting in RV ischemia and further RV dysfunction. In the presence of right coronary stenosis, even mild degrees of pulmonary hypertension can cause ischemic dysfunction. Priebe[10] studied RV free wall function and blood flow in dogs with pulmonary hypertension and subcritical stenosis of the RCA. Right coronary stenosis or pulmonary hypertension alone had no effect on RV blood flow or contractile function. The combination of mild pulmonary

hypertension with RCA stenosis resulted in severe ischemic RV dysfunction and systematic hypotension as right coronary blood flow decreased by 60%. Ischemic RV dysfunction will further limit RV contractility in response to moderate increases in RV afterload if coronary blood flow is limited by obstructive disease or decreased systematic perfusion pressure.

In the presence of right coronary stenosis, even mild degrees of pulmonary hypertension can cause ischemic dysfunction.

Thirdly, RV physiology is interdependent with LV physiology. The pericardium and interventricular septum (IVS) play a vital role in integrating right and left heart function, a relationship termed ventricular interdependence.[11] In compensating for acute afterload increases the RV dilates to maintain stroke volume. If diastolic filling is maintained or augmented with volume therapy, RV dilation will be physically limited by either an intact pericardium or juxtacardiac pressures. The IVS is a thickly muscled wall separating the left and right ventricles. The normal radius of curvature of the IVS is concave toward the LV and convex toward the RV. It is the pressure gradient between the ventricles during systole and diastole that determines the position of this mobile septum at all times in the cardiac cycle. As a result of that shared wall, alterations in the filling of one ventricle can substantially alter the diastolic pressure-volume relationship of the opposite chamber. Multiple studies[12,13] have confirmed that when RV dilation is limited by the pericardium, resulting in increased RVEDP, the IVS shifts towards the LV, reducing the overall size of the LV cavity. The leftward septal shift results in mechanical stiffening of the IVS, directly reducing LV compliance. Therefore, when RV volume is changing significantly and the pericardium is intact, changes in LV end-diastolic pressure will not be a reliable guide even to directional changes of LV end-diastolic volume. Ordinarily, an increase in pulmonary capillary wedge pressure (PCWP) associated with a decreased cardiac output is interpreted by the clinician as diagnostic of LV failure. However, in the circumstance of severe pulmonary hypertension, RVEDV and RVEDP will be significantly increased. This may result in leftward septal shift, decreased LV compliance and LVEDV, but an increased PCWP associated with decreased cardiac output. Right ventricular failure with associated dilation alters the diastolic pressure, geometry and function of the LV.

Monitoring of Right Ventricular Function

Methods to assess RV function of critically ill patients at the bedside have been very limited until recently. Standard electrocardiogram (ECG) monitoring has proven to be relatively insensitive in detecting RV ischemia. Case reports have identified surgical patients with intraoperative RV ischemia not detected by standard ECG or hemodynamic monitoring.[14,15] New ECG lead placement systems have been described that are suitable for detecting RV ischemia. Using radionuclide angiography and echocardiography to correlate RV wall motion abnormalities with ECG changes, Klein et al[16] demonstrated a precordial lead, V_4R, placed in the right fourth intercostal space at the midclavicular line has both high sensitivity (83%) and specificity (77%) for RV ischemia.

In the past, central venous pressure measurement has served as the clinical "gold standard" for bedside monitoring of RV pressure and volume assessment. Central venous pressure (CVP) is a measure of right atrial and RV end-diastolic pressure (RVEDP). While CVP is an unreliable indicator of LV pressures, it has proven a reasonably accurate measure of RVEDP in the absence of tricuspid valve dysfunction. Clinically, intravascular pressures are routinely measured. Using intravascular pressures in isolation to assess ventricular function on either side of the heart is often misleading since the heart fills and ejects, not as a function of absolute intracavitary pressure, but rather transmural pressure. Effective transmural pressure is the pressure inside the vessel or chamber minus the extravascular pressure. Measurement of distending transmural pressure is clinically difficult requiring approximation of the juxtacardiac pressure by an esophageal, intrapleural or pericardial catheter. Each method is invasive with potentially serious complications and is poorly tolerated by alert patients. Therefore, measurement of transmural pressure is not widely applied in clinical practice.

Standard electrocardiogram monitoring has proven to be relatively insensitive in detecting right ventricular ischemia.

Clinicians familiar with the use and interpretation of hemodynamic monitoring are aware of the inaccuracy in using intravascular pressure measurements to assess end-diastolic volumes. Studies have clearly shown that neither PCWP or LVEDP correlate with LV cavity size or volume as assessed by various methodologies.[17-19] In cardiac surgical patients, the change in LV volume was opposite in direction to changes in PCWP and LVEDP in over one-half of the occasions change occurred.[20] Similarly, the CVP correlates poorly with RVEDV,[21] most likely the result of acute ventricular compliance changes and altered juxtacardiac pressures in critically ill patients.

For these patients more direct measurements of RV volume and performance are needed to evaluate RV function. Many of the diagnostic modalities developed to measure LV volumes and ejection fraction, a clinically useful quantitative measurement of ventricular performance, have been adapted to measure similar RV parameters. These technologies include radionuclide angiography, contrast ventriculography and echocardiography. With the exception of echocardiography, these methods are unsuitable for intraoperative or serial,

bedside monitoring. In addition, they require assumptions of RV chamber geometry and contraction in order to estimate the RV volume and ejection fraction. Unlike the spherical LV, the RV cavity does not possess a simple geometric shape or pattern of contraction. This makes the reliability of these estimates questionable.

The anesthesiologist must have a high index of suspicion for patients with right ventricular dysfunction . . .

A new technique, combining the principles of thermodilution and a rapid response thermistor pulmonary artery catheter, which allows bedside serial measurement of RV volumes and RV ejection fraction (RVEF) has been developed and validated in critically ill patients.[22,23] The thermodilution technique obviates the need for assumptions concerning RV shape or contraction. From use of a RV ejection fraction/volumetric catheter, the clinician can obtain the following hemodynamic parameters: cardiac output, RVEF, RVEDV and RV stroke volume, RV pressures as well as PAP and PCWP. With simultaneous RV pressure and volume measurements the clinician is able to differentiate myocardial failure from excessive afterload. Finally, serial measurements of RVEF and RVEDV will allow diagnosis of RV dilation and pathophysiology where augmentation of preload is not only ineffective but detrimental to overall cardiac performance. In many, if not most, critically ill patients, intravascular pressure monitoring with cardiac output measurement alone will not identify these circumstances.

Perioperative Right Ventricular Dysfunction and Failure

Perioperative RV dysfunction or failure should be anticipated in a variety of surgical patients. Right ventricular dysfunction has been demonstrated in patients with blunt trauma, sepsis, acute respiratory failure and pulmonary hypertension, chronic obstructive pulmonary disease, and coronary artery disease or prior right ventricular infarctions. The anesthesiologist must have a high index of suspicion for patients with potential RV dysfunction, since most anesthetics are myocardial depressants and involve the use of mechanical ventilation, both of which can exacerbate any preexisting RV dysfunction.

Because of its anterior and substernal location, the RV is susceptible to indirect injury in trauma. Sutherland et al,[34] demonstrated abnormal RV wall motion and decreased RVEF in 15 of 25 consecutive patients who had sustained blunt chest injuries. Similar studies have identified isolated RV dyskinesis, rather than biventricular dysfunction, as the more common pathophysiology in blunt trauma. Victims of blunt trauma often have other associated injuries requiring urgent surgical correction, so that anesthesiologists will frequently be caring for patients with significant but unsuspected RV dysfunction in this setting. Since many trauma patients are young and without preexisting cardiac disease, depressed RVEF and increasing RVEDV with stagnant RV stroke volume is diagnostic of RV contusion. Eddy et al,[25] excluding patients with prior cardiac disease and those in whom a clinical diagnosis of cardiac contusion was made, placed RV ejection fraction/volumetric catheters in blunt trauma patients early in their course to identify unsuspected RV dysfunction. Despite initially normal cardiac outputs, all patients had abnormally low RVEF and increased RV volumes. Non-survivors had lower RVEF and higher mean PAP than survivors. In this observational study, monitoring RV function was able to distinguish non-survivors from survivors by the absence of improvement in RV performance parameters within the first twelve hours. Intravascular volume augmentation is the primary therapy for hypotensive trauma victims. However, since the contused RV has limited preload recruitability, right ventricular oxygen demands increase secondary to dilation at a time when systemic perfusion may be limited. The potential for RV ischemia and further RV dysfunction can occur in trauma patients during resuscitation using volume expansion. The responses of the RV to therapy predicted patient survival in these patients.

Patients with acute septicemia often require surgical therapy to eliminate the etiological source of sepsis. Myocardial dysfunction has been identified in patients with sepsis and a myocardial depressant factor detected in nearly 50% of patients presenting with septic shock.[26] These patients have a higher PCWP, larger LVEDV and a marked decrease in LVEF during the acute phase of septic shock. Acute septicemia can adversely affect RV contractility as well, even in patients with prior normal myocardial function. Hoffman et al[27] identified unsuspected RV dysfunction in patients with septic shock. After plasma volume resuscitation, these patients had significantly lower RVEF and RV stroke work indices and larger RVEDV than surgical controls. No correlation was found between CVP and RVEDV, confirming the inadequacy of conventional methods to assess RV volumes. A significant negative correlation was found between PVR and RVEF, defining the limited contractile response of a depressed RV to afterload stress. With RV volume monitoring, it was possible to identify the blunted response to volume expansion in these septic patients and a relationship was found between RVEDV and patient survival. Non-survivors showed no improvement in RV function over time with no change from their initially large RVEDV or depressed RVEF. Survivors returned to normal RVEDV and gradually improved RVEF. Comparing survivors to non-survivors showed no predictability on the basis of LV function, but survival seemed to depend on improvement in RV performance. Other investigators have identified a high incidence of significant RV dysfunction in septic patients and concluded that clinical assessment and standard hemodynamic monitoring are insufficient to diagnose this RV failure and guide appropriate parenteral fluid therapy.[28]

Patients with prior RV infarctions

or right coronary artery disease are especially susceptible to perioperative RV failure. Infarction of RV is almost always associated with total occlusion of the RCA. Most clinically significant RV infarctions occur in association with ischemia or infarction of the LV inferior wall and posterior IVS since these areas share a common blood supply under a RCA dominant system. There is a high incidence of RV infarction (19-43%) in patients with acute inferior wall infarctions. Cardiac anesthesiologists frequently care for such patients undergoing coronary artery bypass grafting (CABG) surgery. Hines et al[29] in a group of patients undergoing CABG, noted that those with greater than 90% RCA stenosis are at increased risk for RV ischemia, which often escaped detection by conventional monitoring methods.

Hemodynamic sequelae of clinically significant RV infarction includes systemic hypotension and low cardiac output. The principal pathophysiology is a loss of RV contractility, decreased RVEF and stroke volume and consequently, reduced LV preload. The hallmark of treatment for RV infarctions has been intravascular volume loading. Volume loading can improve global cardiac output in the setting of RV infarction and normal PVR.[30] But, Dell'Italia et al[31] demonstrated that volume infusion in patients with RV infarctions did not improve cardiac index or increase LVEDV despite increasing CVP and PCWP. They speculated that increasing RV cavity size with volume therapy further limited LV filling through the mechanism of septal shift and resulted in higher left-sided filling pressures in the absence of increased LVEDV. In contrast to volume loading, dobutamine augmented RV contractility and resulted in significant improvement in overall hemodynamics.

Life-threatening RV failure is well described during cardiac surgery.[32] Right ventricular failure in this setting may be the result of acute RCA occlusion, inadequate myocardial preservation during the period of ischemic arrest, exacerbation of preexisting pulmonary hypertension by cardiopulmonary bypass (CPB) or protamine-induced catastrophic pulmonary vasoconstriction. Boldt et al[33] studied the vulnerability of the RV during the ischemic arrest period and demonstrated that RV myocardial temperature during normothermic CPB is consistently warmer than any area of the LV, and warmer still in patients with severe RCA stenoses. This warmer temperature correlated with post-CPB RV dysfunction in patients despite revascularization of the RCA. These investigators studied the influence of acute volume loading on RV function and overall hemodynamics immediately after cardiopulmonary bypass.[34] In 8 of the 25 patients studied, acute volume loading to restore PCWP to pre-bypass levels resulted in decreased RVEF, decreased RVSV and cardiac index. In these patients RVEDV increased significantly more than in those patients who responded to volume loading with increased RVEF, increased RVSV and hence a minimal increase in RVEDV. These two groups appeared to be distinguished by the presence (decreased RVEF) or absence (increased RVEF) of severe RCA stenosis despite revascularization in all patients. They concluded that the RV was very susceptible to injury during ischemic arrest in patients with RCA disease due to insufficient myocardial protection. Standard pressure monitoring was inadequate to differentiate patients whose RV function improved with augmentation of preload from those in whom volume loading lead to excessive RV distention, increased wall stress and possible RV ischemia.

Anesthesiologists will also find themselves caring for patients with chronic obstructive pulmonary disease,[35] adult respiratory distress syndrome,[36] or those undergoing positive end-expiratory pressure therapy[37] in the perioperative period, all of whom have been identified as susceptible to RV failure.

Management of Perioperative Right Ventricular Failure

Management of the patient with RV failure is undergoing rethinking in light of new information on RV function. Previously, volume expansion has been the mainstay of treatment for situations of RV failure. Preload augmentation does increase RV myocardial fiber stretch and will lead to enhanced stroke volume if the RV is not already stretched beyond an optimal point. Dilation is the major compensatory mechanism for augmenting RV contractility and will often be effective in improving overall cardiac output under conditions of normal RV afterload. However, volume therapy has often proven insufficient to restore overall circulatory status in experimental and clinical circumstances of RV failure.[31,34,38] It is now apparent that preload recruitability has a limited therapeutic role in RV failure associated with a pulmonary hypertension.

For surgical patients sustaining right ventricular failure associated with increased pulmonary vascular resistance, management begins by avoiding excessive myocardial depressant anesthetics.

For surgical patients sustaining RV failure associated with increased PVR, management begins by avoiding excessive myocardial depressant anesthetics. The anesthesiologist must treat intraoperative hypoxemia, hypercarbia or acidosis which will further increase PVR. Inotropic augmentation with or without concomitant use of a vasodilator is efficacious therapy in this setting. Therapy must be directed at restoring the pump function of the RV by either direct inotropic support or reducing right ventricular work. Dell'Italia et al[31] demonstrated the superiority of dobutamine over volume loading alone or volume loading with afterload reduction using nitroprusside, in patients with severe RV infarctions. In cardiac surgical patients, where RV failure is most commonly associated with LV failure and increased PVR, the combination of inotropic and vasodilator therapy often provides optimal hemodynamics. Because of their combined ino-

tropic and vasodilating effects, amrinone and isoproterenol have a rational basis for early use in patients with RV failure and pulmonary hypertension. There is however, no evidence either is more efficacious than other inotropes. In this setting, it would be desirable to have a selective pulmonary vasodilating agent to avoid any exacerbation of preexisting systemic hypotension and jeopardize RCA perfusion. In the dog prostaglandin E_1 (PGE_1), a potent vasodilator, acts as a selective pulmonary vasodilator if given into the right heart on the basis of nearly 100% first pass metabolism in the lung. D'Ambra et al[39] demonstrated the efficacy of this new agent to dilate the pulmonary vasculature and reverse life-threatening RV failure in cardiac surgical patients in whom prior inotropic and non-selective vasodilator therapy had been insufficient. However, in the human lung, PGE_1 does not have complete first pass metabolism and produces unacceptable systemic hypotension. Implementation of therapy requires right heart infusion of PGE_1 in combination with a norepinephrine infusion into the left atrium.

Right ventricular failure is frequently associated with arterial hypotension or RCA disease. In this setting the need to increase RV coronary blood flow is critical to improving overall RV function. A number of investigators [38,40-41] have successfully reversed ischemic dysfunction with vasoconstrictor agents. If RV failure is initially caused by or later exacerbated by RV ischemia any proposed therapeutic plan must include increasing systemic pressure and hence RV coronary blood flow.

Finally, in cardiac surgical patients the use of mechanical ventricular assist devices has been successful in treating RV failure.[42,43] Pulmonary arterial balloon counterpulsation has had modest success in this area[35] and others have employed RV bypass to treat isolated RV failure. The ring atrium is cannulated for venous drainage and return can be either to the pulmonary artery or the left side of the heart. A variety of pumps have been used, including the vortex (Biomedicus), and an oxygenator can be placed in circuit if needed. When the RV assist pump is used to treat isolated RV failure, most patients have survived. However, in the setting of biventricular failure requiring left and right heart mechanical support the results have been poor.[44]

In summary, right ventricular function is currently undergoing an unprecedented period of scientific interest. Previously unrecognized patient populations at risk for RV failure have been identified and new management strategies are already appearing to assist anesthesiologists and all clinicians who care for these patients.

References

1. Starr I, Jeffers WA, Meade RH. The absence of conspicuous increments in venous pressure after severe damage to the right ventricle of the dog, with a discussion of the relation between clinical congestive failure and heart disease. Am Heart J 3:291-301, 1943.
2. Haupt H, Hutchus A, Moore A. Right ventricular infarction: Role of the moderator band artery in determining infarct size. Circ 67:1268-1272, 1983.
3. Armour JA, Pace JB, Randall WC. Interrelationship of architecture and Function of the right ventricle. Am J Physiol 218:174, 1970.
4. Maughan WL, Shoukas AA, Sagawa K, Weisfeldt ML. Instantaneous pressure-volume relationship of the canine right ventricle. Circ Res 44:309, 1979.
5. Taylor RR, Covell JW, Sonnenblick EH, Ross J. The dependence of ventricular distensibility in the filling of the opposite ventricle. Am J Physiol 213:711, 1967.
6. Janicki JS, Weber KT. The pericardium and ventricular interactions, distensibility and function. Am J Physiol 238:H494, 1980.
7. Hurford We, Barlai-Kovach M, Strauss HW, Zapol WM, Lowenstein E. Canine biventricular performance during acute progressive pulmonary microembolization: regional myocardial perfusion and fatty acid uptake. J Crit Care 2:270-281, 1987.
8. McFadden ER, Braunwald E. Cor pulmonale and pulmonary thromboembolism. In Braunwald E (ed.): Textbook of Cardiovascular Medicine. Philadelphia, WB Saunders, 1980, pp. 1643-1680.
9. Calvin JE. Right ventricular afterload mismatch during acute pulmonary hypertension and its treatment with dobutamine: a pressure segment length analysis in a canine model. J Crit Care 4:251-265, 1989.
10. Priebe HJ. Myocardial ischemia in a canine model of pulmonary hypertension and right coronary artery stenosis. Anesthesiology 72:517-525, 1990.
11. Laver MB, Strauss WH, Robost GM. Herbert Shubin Memorial Lectures. Right and left ventricular geometry: Adjustments during acute respiratory failure. Crit Care Med 7:509-516, 1975.
12. Brinker J, Weiss J, Lappe D, et al. Leftward septal displacement during right ventricular loading in man. Circulation 61:626-633, 1980.
13. Bemis CE, Serur JR, Borkenhagen D, et al. Influences of right ventricular filling pressure on left ventricular pressure and dimension. Circ Res 34:498-504, 1974.
14. Hines R, Barash P. Intraoperative right ventricular dysfunction detected with a right ventricular ejection fraction catheter. J Clin Monitoring 2:206-208, 1986.
15. Trager MA, Feinberg BI, Kaplan JA. Right ventricular ischemia diagnosed by an esophageal electrocardiogram and right atrial pressure tracing. J Cardiothor Anesth 1:123-125, 1987.
16. Klein HO, Tordjman T, Ninio R, et al. The early recognition of right ventricular infarction: Diagnostic accuracy of the electrocardiographic V_4R lead. Circulation 67:558-565, 1983.
17. Raper R, Sibbald WJ. Misled by the wedge? The Sean-Ganz catheter and left ventricular preload. Chest 89:427-434, 1986.
18. Calvin JE, Driedger AA, Sibbald WJ. Does the pulmonary capillary wedge pressure predict left ventricular preloading in critically ill patients? Crit Care Med 9:437-443, 1981.
19. Hansen RM, Viquerat CE, Matthay MA, et al. Poor correlation between pulmonary arterial wedge pressure and left ventricular end-diastolic volume after coronary artery bypass graft surgery. Anesthesiology 64:764-770, 1986.
20. Douglas PS, Edmunds LH, Sutton MS, et al. Unreliability of hemodynamic indexes of left ventricular size during cardiac surgery. Ann Thorac Surg 44:134, 1987.
21. Martyn JAJ, Snider MT, Farago LF, Burke JF. Thermodilution right ventricular volume. A novel and better predictor of volume replacement in acute thermal injury. J Trauma 21:619-624, 1981.
22. Kay H, Afshan M, Barash PG, et al. Measurement of ejection fraction by thermal dilution techniques. J Surg Res 34:337-346, 1983.
23. Dhainault JF, Brunet F, Monsallier JF, et al. Bedside evaluation of right ventricular performance using a rapid computerized thermodilution method. Crit Care Med 15:148-152, 1987.

[24] Sutherland GR, Calvin JE, Driedger AA, et al. Anatomic and cardiopulmonary responses to trauma with associated blunt chest injury. JH Trauma 21:1-8, 1981.
[25] Eddy AC, Rice CL, Anardi DM. Right ventricular dysfunction in multiple trauma victims. Am J Surg 155:712-715,. 1988.
[26] Reilly JM, Cunnion RE, Burch-Whitman C, et al. A circulating myocardial depressant substance is associated with cardiac dysfunction and peripheral hypoperfusion (lactic acidemia) in patients with septic shock. Chest 95:1072-1080, 1989.
[27] Hoffman MJ, Greenfield LJ, Sugerman HJ, Tatum JL. Unsuspected right ventricular dysfunction in shock and sepsis. Ann Surg 198:307-318, 1983.
[28] Kimchi A, Ellrodt AG, Berman DS, et al. Right ventricular performance in septic shock: A combined radionuclide and hemodynamic study. J Am Coll Cariol 4:945-951, 1984.
[29] Hines R, Barash P. The right ventricle: Master or servant? Anesthesiology 61:A8, 1984.
[30] Loepz-Sendon J, Coma-Canella I, Vinuelas-Adamez J. Volume loading in patients with ischemic right ventricular dysfunction. Eur Heart J 3:329-338, 1981.
[31] Dell'Italia L, Starling M, Blomhardt R, et al. Comparative effects of volume loading, dobutamine, and nitroprusside in patients with predominant right ventricular infarction. Circulation 72:1327-1335, 1985.
[32] Spence PA, Weisel RD, Salerno TA. Right ventricular failure: Pathophysiology and treatment. Surg Clin North Am 65:689-697, 1985.
[33] Boldt J, Kling D, Dapper F, Hempelmann G. Myocardial temperature during cardiac operation: Influence on right ventricular function. J Th CV Surg 100:562, 1990.
[34] Boldt J, Kling D, Moosdorf R, Hempelmann G. Influence of acute volume loading on right ventricular function after cardiopulmonary bypass. Crit Care Med 17:518, 1989.
[35] Jezek V, Schrijen F, Sadoul P. Right ventricular function and pulmonary hemodynamics during exercise in patients with chronic obstruction broncho-pulmonary disease. Cardiology 58:20-31, 1973.
[36] Brunet F, Dhainaut JF, Devaux JY, et al. Right ventricular performance in patients with acute respiratory failure. Intens Care Med 14:474-477, 1988.
[37] Schulman DS, Biondi J, Matthay RA. Effect of positive end-expiratory pressure on right ventricular performance: Importance of baseline right ventricular function. Am J Med 84:57-67, 1988.
[38] Ghignone M, Girling L, Prewitt RM. Volume expansion versus norepinephrine in treatment of a low cardiac output complicating an acute increase in right ventricular afterload in dogs. Anesthesiology 60:132-135, 1984.
[39] D'Ambra M, LaRaia P, Phellen D, Lappas D. Prostaglandin E_1-a new therapy for refractory right heart failure and pulmonary hypertension after mitral valve replacement. J Thorac Cardiovasc Surg 89:567-572, 1985.
[40] Laver MB. Myocardial ischemia: Dilemma between information available and information demand. Br Heart J 50:222-230, 1983.
[41] Vlahakes GJ, Turley K, Hoffman JIE. The pathophysiology of failure in acute right ventricular hypertension: Hemodynamic and biochemical correlations. Circulation 63:87-95, 1981.
[42] Parr GVS, Pierce WS, Rosenberg G. Waldhausen JA. Right ventricular failure after repair of left ventricular aneurysm. J Thorac Cardiovasc Surg 80:L79-84, 1980.
[43] O'Neill MJ, Pierce WS, Wisman CB, et al. Successful management of right ventricular failure with the ventricular assist pump following aortic valve replacement and coronary bypass grafting. J Thorac Cardiovasc Surg 87:106-111, 1984.
[44] Pierce WS, Parr GVS, Myers JL. Ventricular-assist pumping in patients with cardiogenic shock after cardiac surgery. N Engl J Med 305:1606-1610, 1981.

RHODE ISLAND COMPUTERIZED IMAGING, INC.

Cat Scan Facility
401•751•1110

weekdays
7 am - 5 pm

- Evening appointments for contrast studies
- Medicare, Ocean State
  Rhode Island Blue Cross/Blue Shield approved
- Board Certified Radiologist

Located in: Atwood Medical Center
Suite LL3
1524 Atwood Avenue
Johnston, RI 02919

QUESTION:

WHAT ARE THE THREE MOST IMPORTANT THINGS TO CONSIDER WHEN CHOOSING AN INSURANCE AGENCY?

ANSWER:

EXPERIENCE, EXPERIENCE, EXPERIENCE

INSURANCE SINCE 1879

STARKWEATHER & SHEPLEY INC. - (401) 421-6900

Morton Smith, Inc. - (401) 861-6800

155 South Main Street
Providence, Rhode Island 02903

Specialty Medical Education in Anesthesiology

Ronald L. Fischer, MD, FCCP

One has to study a great deal to know a little.[1]

The professional development of qualified physician anesthesiologists and nurse anesthetists requires an extensive commitment on the part of society as well as the individuals who undergo the training process. Anesthesiology is the branch of medicine that most effectively bridges the gap between the basic and clinical medical sciences. The discipline requires an advanced expertise in pharmacology and physiology, as well as mastery of ventilatory control, evaluation of respiratory exchange, cardiovascular monitoring and management as well as care of the comatose. Additionally, neurologic assessment and differentiation of subtle changes in levels of consciousness, fluid and electrolyte management, transfusion and antimicrobial therapy all fall within its purview.[2] Practitioners of the specialty have wide exposure and interface with many disciplines in the surgical, medical and pediatric fields. As such, the educational process is lengthy, arduous and continually challenging.

Ronald L. Fischer, MD, FCCP, is Chief, Department of Anesthesiology and Director of the School of Nurse Anesthesia at The Memorial Hospital of Rhode Island and Clinical Assistant Professor, Brown University, Providence, Rhode Island.

The American Board of Anesthesiology (ABA) was established in 1937 to organize a certification process for physicians practicing in the field of anesthesiology. Similarly, the American Association of Nurse Anesthetists (AANA) was established in 1935 and charged with the credentialization and certification of nurse anesthetists. These two organizations have been entrusted with the responsibility for educational training requirements and for continuing educational programs.

In an effort to maintain the highest standards of medical practice, the ABA has given definition to anesthesiology[3] as follows:

1. The assessment of, consultation for, and preparation of patients for anesthesia.
2. The provision of insensibility to pain during surgical, obstetric, therapeutic and diagnostic procedures, in the management of patients so affected.
3. The monitoring and restoration of homeostasis during the perioperative period, as well as homeostasis in the critically ill, injured or otherwise seriously ill patient.
4. The diagnosis and treatment of painful syndromes.
5. The clinical management and teaching of cardiac and pulmonary resuscitation.
6. The evaluation of respiratory function and application of respiratory therapy in all its forms.
7. The supervision, teaching and evaluation of performance of both medical and paramedical personnel involved in anesthesia, respiratory and critical care.
8. The conduct of research at the clinical and basic science levels to explain and improve the care of patients.
9. The administrative involvement in hospitals, medical schools and outpatient facilities necessary to implement these responsibilities.

Additionally, the Board has listed the following goals:[4]

A. To establish and maintain criteria for the designation of a consultant anesthesiologist.

ABBREVIATIONS USED:
AANA: American Association of Nurse Anesthetists
ABA: American Board of Anesthesiology
ACGME: Accrediting Council for Graduate Medical Education
CRNA: Certified Registered Nurse Anesthetist
GMENAC: Graduate Medical Education National Advisory Committee
HHS: Health and Human Service
PGY-1: Post graduate year 1

B. To inform the Accreditation Council for Graduate Medical Education (ACGME) concerning the training required of individuals seeking certification as such requirements relate to residency training programs in anesthesiology.

C. To establish and conduct those processes by which the Board may judge whether physicians who voluntarily apply should be issued certificates indicating that they have met the required standards for certification as a consultant in anesthesiology. A consultant anesthesiologist possesses adequate measures of knowledge, judgement, clinical and character skills, and personality suitable for assuming independent responsibility for patient care, for serving as an expert with the ability to deliberate with others providing advice and opinions in areas related to the practice of anesthesia including all subspecialties and for functioning as the leader of the anesthesia care team.

D. To establish and conduct those processes by which the Board may judge whether physicians who voluntarily apply should be issued certificates indicating that they have met the required standards for subspecialty certification in a designated subdiscipline of anesthesiology.

To serve the public, medical professions, hospitals and medical schools by preparing for publication lists of physicians certified by the Board.

The Twelve-Year Curriculum

The educational requirements for certification by the ABA as a consultant anesthesiologist have recently been expanded to entail a full twelve-year preparatory and training process. Traditionally commencing with a four-year premedical undergraduate baccalaureate program, the process continues with a general medical education leading to a Doctor of Medicine degree, followed by four additional years of post-doctoral specialty training in anesthesiology.

The four-year post-doctoral component (residency) is further subdivided into a "Clinical Base" year (internship) devoted to clinical training in areas other than anesthesiology.[4] This initial post-graduate year (PGY-1) is frequently devoted to education and service in internal medicine, surgery, pediatrics, obstetrics or combinations of the above. Thus, the physician at this point has broadbased general medical experience before beginning specialty education in anesthesiology. Subsequently, the candidate undergoes two years of "Basic Anesthesia Training" including subspecialty experiences in obstetric, pediatric, cardiothoracic, neurologic and ambulatory anesthesia. Additional experience is obtained in intensive and critical care medicine, regional anesthesia and pain management. Didactic and clinical instruction are provided, with the physician acquiring increasing levels of clinical acumen, decision making responsibility and judgmental capability.

The final year of the process constitutes "Advanced Anesthesia Training" which includes experience in the "more difficult or complex anesthetic procedures".[4] During this final phase of specialty training, the physician will consummate his expertise in the application of clinical judgment and intricate decision making. The resident physician further develops sophisticated abilities to function as an expert medical specialist in anesthesiology. The result is a highly trained, extensively educated and accomplished physician qualified to independently practice anesthesiology.

At the completion of this twelve-year curriculum, the physician is considered to be board eligible only if he remains an active candidate in the examination system for certification by the ABA. Upon successful completion of both the written and oral sections of the Board examination, the candidate is certified as a Diplomate of the ABA. The Board endeavors to identify those candidates who possess the knowledge, judgment, communicative and decision-making skills that are considered essential for the Diplomate to function as a consultant in anesthesiology and as the leader of the anesthesia care team in considering the objective and subjective examination performance of candidates for specialty board certification.

These requirements (for Board eligibility status) are among the most stringent and rigorous of any specialty board . . .

If the candidate is unsuccessful three times in the Board examination or is more than twelve years removed from residency, qualifications for admission to the examination process must be reestablished, occasionally necessitating the return to residency for an additional twelve months of clinical training in an ACGME accredited program. Therefore, Board Eligible Status is not conferred indefinitely, as is widely assumed. These requirements are among the most stringent and rigorous of any specialty board affiliated with the American Board of Medical Specialists.

Manpower Needs

Because anesthesia is an essential and pivotal service in maintaining the occupancy of hospital beds and the functioning of operating rooms, an insufficient supply of anesthesia practitioners often results in major difficulties for hospitals and the quality of patient care. The establishment of a large number of ambulatory surgical centers has contributed to an increas-

Table 1. **Increased Application to Anesthesia Residencies**[14]

Year	1978	1980	1982	1983	1984	1985
No. Positions	448	518	507	437	427	385
No. Applications/position	1.4	2.0	4.6	5.0	6.0	6.5
% Positions Filled	42%	50%	76%	83%	90%	93%

ing need for both physician anesthesiologists and nurse anesthetists due to greater decentralization of services. This effect has also been seen with the expanded role of anesthesiology practitioners in obstetric and intensive care areas.

The Graduate Medical Education National Advisory Committee (GMENAC) report in 1980 concluded that anesthesiology would remain an undersupplied specialty throughout the 1990s.[5] Young physicians in the process of training and selecting their specialties were influenced by this study as well as the perception of scientific challenge and technological sophistication in the field. A remarkable period of growth followed almost immediately and a 30% increase in the supply of anesthesiologists occurred over the next 6 years.

Using the GMENAC adjusted needs-based model for projecting physician requirements, Bowman et al reviewed the specialty of anesthesiology in 1983 and found that by 1990 this nation would need approximately 22,143 anesthesiologists.[6] This was subdivided as follows: 16,500 anesthesiologists for surgery related needs; 811 for obstetrics; 830 for intensive care; 200 for pain management; 3,000 for non-faculty teaching, research, and administration; and approximately 2,500 for faculty. An adjustment to these figures was made to account for approximately 1,600 full-time equivalent anesthesiologists for patient care that were provided by faculty. The projected total supply for 1990 was estimated to be 19,450 which was expected to result in a shortage of 2,700 anesthesiologist; therefore, anesthesiology was to be one of the few specialties in medicine that would continue to have a shortage of physicians. In part to compensate for this, the number of reported residency positions offered each year increased in anesthesiology from 2,800 in 1980 to over 5,400 in 1991.

In 1985, Kelly and coworkers reviewed the number of applications per available anesthesia residency position and found an increase of over 400% as shown in Table 1.[7] The successful recruitment of physicians to fill these positions has more than doubled, with 93% of positions filled by 1985, up from only 42% in 1978. These trends have not only continued, but have even begun to result in many applications from physicians with PhDs or previous specialty boards in other fields such as internal medicine, pediatrics or surgery. A 400% increase in the number of applications per residency position constitutes one of the highest success rates amongst all medical specialties. This may reflect that the values and interests in the applicant group may have shifted to a greater interest in physiology and pharmacology, as well as an awareness of the diverse opportunities that are available for anesthesiologists as well as the good quality of life that many medical students have come to perceive as a well-known by-product of this profession.

To meet the needs of anesthesiology health care, the number of graduating

Table 2. **The Most Important Educational Items Ranked by Graduate Anesthesiologists and Medical Students**[12]

Item	Rankings	
	Anesthesiologists	Students
Which medication to discontinue preoperatively	1	1
Peri-op management of cardiovascular disease	2	5
Management of airway in unconscious patient	3	25
Interpretation of arterial blood gases	4	21
Influence of concurrent medications	5	6
Endotracheal intubation	6	9
Cardiopulmonary resuscitation	7	24
Peri-op management of hypertension	8	17
Influence of preexisting disease on management	9	22
Indications for endotracheal intubation	10	2
Perioperative fluid and electrolyte therapy	11	13
Treatment of shock	12	3
Perioperative management of diabetes	13	23
Ventilation using a bag and mask	14	4
Blood and component therapy	15	40

Table 3. **The Fifteen Least Important Educational Items Ranked by Graduate Anesthesiologists and Medical Students**[12]

Item	Rankings	
	Anesthesiologists	Students
Establish and interpret evoked potential monitors	84	82
Physics and mechanics of apparatus	83	83
Interpretation of EEG and processed EEG monitors	82	77
Establish and manage plexus anesthesia	81	60
Establish and manage IV regional anesthesia	80	57
Anesthesia for cesarean section	79	75
Fiberoptic laryngoscopy & bronchoscopy	78	65
Obtaining consent	77	67
Analgesia for labor	76	72
Anesthesia for vaginal delivery	75	74
Establish and manage field blocks	74	70
Evaluation of the pain patient	73	64
Physiology of chronic pain	72	66
Treatment of chronic pain	71	62
Influence on perianesthetic period of lifestyle	70	84

physician anesthesiology residents has increased over the past decade from approximately 800 to 1,200 per year.[8,9] This, in large measure, has closed the gap between the projected physician needs versus supply. In addition to the quantity of applicants that are applying to anesthesiology residencies, the quality of applicants also has appeared to increase significantly. The past decade has also witnessed a major improvement in the popularity and desirability of anesthesiology as a career choice of young physicians.

The past decade has witnessed a major improvement in the popularity and desirability of anesthesiology as a career choice of young physicians.

Table 4. **Ranking of Curriculum Areas by Anesthesiologists and Students**[12]

Curriculum Area	Rankings	
	Anesthesiologists	Students
Cardiopulmonary Resuscitation	1	1
Blood, Fluid and Electrolytes	2	9
Intensive Care	3	3
Perioperative Management of Diseases	4	7
Intravenous Cardiovascular Drugs	5	2
Care of the Unconscious Patient	6	5
Preoperative Evaluation	7	11
Pharmacology of Anesthetic Agents	8	8
Premedication	9	6
Administration of General Anesthesia	10	4
Establishing and Interpreting Monitors	11	10
Local Anesthesia	12	12
Chronic Pain	13	13
Obstetric Anesthesia	14	14
Physics and Mechanics of Apparatus	15	15

As described above, the vacancy rates for anesthesia residency positions have fallen dramatically, while simultaneously a dramatic increase in the number of applicants per position has also occurred. The result has been the achievement of a near balance in the last decade of the 20th century in terms of the number of available anesthesiologists in proportion to the number that are needed. There still remains a significant geographic maldistribution of anesthesiologists, where as the metropolitan, suburban, and western states tend to be the most heavily supplied, while the rural, southern, and midwestern states still tend to have significant shortages of anesthesia care providers.[9]

To meet the future national manpower needs in anesthesia health care, there are currently approximately 155 accredited residency training programs and 80 nurse anesthesia educational programs. The number graduating from the latter has declined from 1100 per year to 600 as described by the Department of Health and Human Services in the report "Study of Nurse Anesthetist Manpower Needs".[10] This study concluded that the present national supply of 20,000 nurse anesthetists falls over 5,000 short of the current need for 25,000. The HHS report also predicted a requirement for over 35,000 CRNAs by 2010. To accommodate these requirements, both the creation and expansion of new nurse anesthesia training programs will be necessary.

The Content of Specialty Training in Anesthesiology

The success of recruiting medical students to select anesthesiology as a career choice has also been facilitated by the participation of anesthesiology faculty in the basic science curriculum during the first years of medical school. In turn, medical students have developed a greater understanding and appreciation of the content of the anesthesiologist's knowledge base and repertoire or clinical skills.

As demonstrated in Tables 2-4, students tend to have a higher regard for learning psychomotor skill items, while experienced practitioners tend to value the cognitive aspects of perioperative medical management and applied pharmacology of anesthetic agents, as well as techniques of anesthetic administration.[12] From Table 2 one can see that the experienced anesthesiologist placed a much higher value on subjects such as management of the airway in an unconscious patient, interpretation of blood gases, the perioperative management of hypertension, and especially the influence of preexisting heart disease on anesthetic management. Nevertheless, medical students seem to be coming into earlier contact with practicing anesthesiologists and therefore are learning to appreciate a need for the knowledge and skills that constitute the medical specialty of anesthesiology.

Anesthesiology is widely regarded as one of the most stressful specialties in the medical profession. Studies fortunately show that this stress can be attenuated by advanced training. Toung in 1985 found that during the most stressful stages of anesthetic induction, residents in anesthesiology experience an average 70% increase in heart rate, and during the same stage of the procedure, an experienced staff anesthesiologist would sustain an average increase in heart rate of only 35%.[13] Similar studies concur that following the development of clinical skill and confidence, the stress associated with administering anesthesia becomes more manageable and controllable.

Resident physicians said students in the process of specialty training occasionally encounter significant problems affecting their overall clinical performance. Rhoton and coworkers used a daily evaluation system to identify these difficulties at five different institutions and to provide appropriate counseling.[14] They found the most frequent incidents were related

to efficiency, organization, conscientiousness, technical skills and fund of knowledge. The authors also noted a pattern of under-confidence in the first three months of training, while beyond this point overconfidence was predominant. Indeed, the perception of many supervisory and faculty member indicates overconfidence on the part of trainees to constitute one of the greatest challenges to the simultaneous goals of clinical instruction and safe patient care.

Controversy has long existed regarding 24 hour on-call experiences for physicians in anesthesiology training programs. Although this can represent an excellent learning opportunity, providing invaluable exposure to clinical medicine, the risks to the patient as a result of performance deterioration may outweigh the benefits to the resident or student. A study in 1985 by Klose et al, evaluated the psychomotor performance of anesthesiology residents by using information processing tests which were administered on five consecutive days following the period of sleep deprivation.[15] There were subtle, significant differences between certain aspects of the performance of various psychomotor and information processing tests, but no significant deterioration in their overall performance.

Future Trends in Education

The direction of future program development in the field of anesthesiology involves incorporating the trend towards greater subspecialization in the academic curriculum. In 1985, the three year post-graduate anesthesiology curriculum was expanded to a full four-year residency program. There has been considerable debate as to whether this fourth post-graduate year should consist of a year of subspecialization, ie, in the areas of cardiac, obstetrical, pain management, pediatric, intensive care, or neurosurgical anesthesia. Some program directors have elected to treat the fourth post-doctoral year much like a "fellowship", with specific focus and specialization in one of the above areas. Many other program directors, however, have viewed the fourth post-doctoral year as an additional year of residency with further exposure to the broad spectrum of surgical pathology being preferable to narrow subspecialization experiences. Some anesthesiologists have undertaken four years of post-doctoral training (including a fourth year of general anesthesiology), and have elected to train for a fifth post-doctoral year in order to gain the subspecialty experience that they consider important for their future careers. Thus, the post-doctoral anesthesiology curriculum in some cases has been expanded to not only four full years, but to a fifth year as well.

> ***For the things we have to learn before we can do them we learn by doing them.***[11]

Future development for nurse anesthesia educational programs will require conversion to a master's degree format by 1998, as mandated by the AANA Council on Accreditation. Presently, about one-third of all programs are exclusively hospital-based without university affiliation, and offer a certificate or diploma in lieu of an academic degree.[16] The master's format would seem appropriate since the overall educational time commitment and program content for a graduate nurse anesthetist is now six years which is substantially equal to or greater than that of other master degree recipients. Therefore, the nurse anesthetist will gain well-deserved recognition of the advanced level of academic and professional accomplishment they have earned.

The selection of the particular discipline in which the master's degree for nurse anesthetists will be earned depends partially on the individual preference of the candidate as well as the capability of the degree granting institution. Some institutions are prepared to award a master's in anesthesia science. Others confer this degree in biology, nursing, or education. The AANA Council on Accreditation has already established a requirement that nurse anesthesia faculty members must have a master's at a minimum. Indeed, a considerable number of CRNA program directors are advancing their education on the doctoral level, which would appear to greatly strengthen the caliber of teaching and leadership available for the student of nurse anesthesia.

Conclusion

In the state of Rhode Island, we are fortunate to have formalized training programs in anesthesiology for both physicians and nurses. The Rhode Island Hospital currently contributes to the professional development of resident anesthesiologists who rotate from the University of Massachusetts. This endeavor is expected to mature into a fully accredited, independent residency program in two or three years. Furthermore, The Memorial Hospital of Rhode Island and St. Joseph's Hospital both have long-established, highly successful schools of nurse anesthesia. Following a four-year undergraduate baccalaureate degree in nursing or biology, these two year programs have a proven track record of graduating professional nurse anesthetists who are competent, well-qualified and of enormous benefit to our patients.

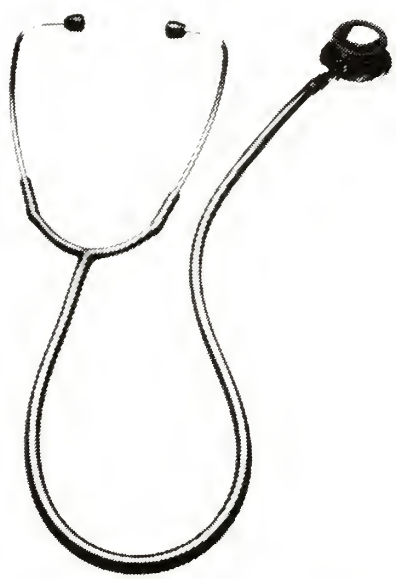
It is essential to the health care delivery system to expand and improve the profession of anesthesiology through continued maintenance and support of our educational and training resources.

References

1. deSecondat, C. Penses et Fragments Inedits de Montesquieu 1899; Chapter 1.
2. Dripps RD, Eckenhoff JE, Vandam LD. Introduction to Anesthesia: The Principles of Safe Practice, 7th ed. Philadelphia: WB Saunders, 1988.
3. Miller RD. A History and the Scope of Anesthesia Practice in Anesthesia, 2nd ed. New York, Churchill Livingstone, 1986.
4. The American Board of Anesthesiology Booklet of Information, Hartford, 1991.
5. Summary Report of the Graduate Medical Education National Advisory Committee to the Secret, Department of Health and Human Services. DHHS Pub. No. (HRA)

91-651. Hyattsville (MD), Health Resources Administration, 1980.
6 Bowman MA, Katzoff JM, Garrison LP, Wills J. Estimates of Physician Requirements of 1990, for the Specialties of Neurology, Anesthesiology, Nuclear Medicine, Pathology, Physical Medicine and Rehabilitation, and Radiology. A Further Application of the GMENAC Methodology. JAMA 1983; 250:2623-2627.
7 Kelly SM, Mulroy MF. Senior Medical Student Applicants for Four-Year Anesthesia Residencies: More and Better? Anesthesiology 1985; 63:A486.
8 Zaidan JR. Impact of ABA Requirements on Residency Program Structure and Manpower. Anesthesiology 1986; 65:A474.
9 Orkin FK. Anesthesiology Manpower 1990. A Tale of Three Trends. ASA Newsletter, May 1990.
10 US Department of Health and Human Services, Public Health Service. National Institutes of Health, National Center for Nursing Research. 1990. Study of Nurse Anesthetist Manpower Needs.
11 Aristotle, Nichomachean Ethics, Book II, Chapter 1, 4th Century BC.
12 Polk SL. What Should We Teach about Anesthesiology in Medical School: Results of a Needs Assessment Survey. Anesthesiology 1987; 67:A557.
13 Toung T, Donham RT, Rogers MC. Anesthesiology Training and the Stress of Giving Anesthesia. Anesthesiology 1985; 63:A490.
14 Rhoton F, Barnes A, Flashburg M, Ronai A, Springman S. The Most Frequent Clinical Performance Problems During Residency Training in Anesthesiology at Five Institutions. Anesthesiology 1988; 69:A795.
15 Klose KJ, Wallace-Barnhill GL, Craythorne NWB. Performance Test Results for Anesthesia Residents over Five-Day Week Including in On-Call Duty. Anesthesiology 1985; 63:A485.
16 American Association of Nurse Anesthetists, 1990. National Commission on Nurse Anesthesia Education. Chapter II:9.

PHYSICIANS: A BROADENING EXPERIENCE WITH FLEXIBLE SCHEDULING.



As part of our Medical Department's National Army Augmentation Detachment (NAAD) we can adjust schedules to fit your requirements while you reap the benefits of valuable additional training.

You will also have ample opportunities to explore other phases of medicine, take advantage of developmental programs like the Combat Casualty Course and Basic Airborne or Air Assault training, participate in a variety of other programs with medical leaders from all over the country, as well as enjoy the rank and privileges of an Army officer.

Find out just how accommodating we can be for a small portion of your valuable time. Contact an Army Reserve Medical Counselor for details. Just call collect or write:

CAPTAIN JOHN GRIMES
203-624-5325

ARMY RESERVE MEDICINE.
BE ALL YOU CAN BE.

CREATE A MEDICAL BREAKTHROUGH.

Become an Air Force physician and find the career breakthrough you've been looking for.

- No office overhead
- Dedicated, professional staff
- Quality lifestyle and benefits
- 30 days vacation with pay per year

Today's Air Force provides medical breakthroughs. Find out how to qualify as a physician or physician specialist. Call

USAF Health Professions
Toll Free
1-800-423-USAF

AIR FORCE

RHODE ISLAND

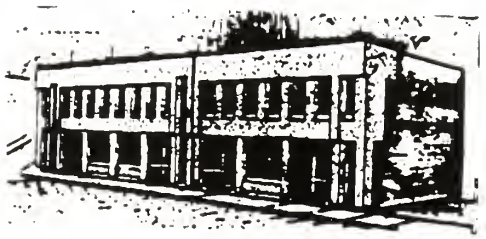
Excellent opportunities in urgent care facilities for career oriented physicians. Competitive salary and benefits.

(401) 943-4540

or send CV to:

Anthony Migliaccio, MD
Medical Director
Northeast Health Care, Inc.
495 Atwood Avenue
Cranston, RI 02920

CONDOMINIUMS
FOR SALE OR LEASE



845 NORTH MAIN STREET
PROVIDENCE, RI

- Professional Office and Retail Space
- Convenient Access to I-95
- Minutes from downtown Providence, the Hospitals and Universities
- Ample On-Site Parking

CONTACT: CINDY MORSE, CCIM
PETER M. SCOTTI & ASSOCIATES
60 Ship Street, Providence, RI 02903
401-421-8888

CCIM

HEALTH BY NUMBERS

Rhode Island
Department of Health
Barbara A. DeBuono, MD, MPH
Director of Health

Health Insurance Coverage in Rhode Island, 1990-1991

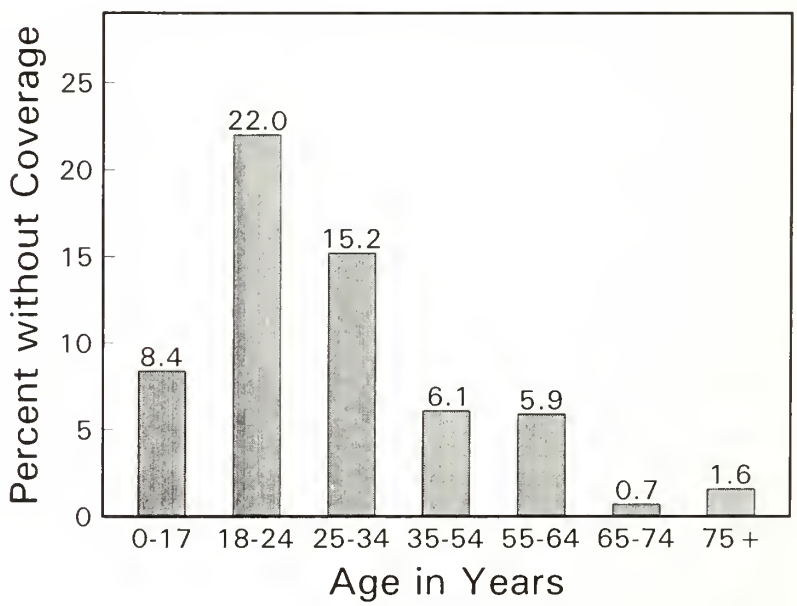
Rhode Island's population has traditionally enjoyed rates of health insurance coverage that are higher than those of most other states. The state's recent surge in unemployment and the increasing cost of private group health insurance have raised concern for this key measure of access to health care. In its most recent statewide Health Interview Survey, which was conducted from November 1990 through February 1991, the Department used telephone interviews to collect information on the health of 6,536 persons living in 2,588 randomly selected households throughout the state. Special attention was given to collecting accurate data on health insurance coverage during the survey.

Estimates from the Survey are that 9.2% of the state's population, or about 92,000 persons, have no public or private health insurance coverage, up from the 1985 estimate of 8.4%. Non-coverage was found to vary greatly by age, with young adults being least likely to have insurance and the elderly exhibiting nearly universal coverage through the Medicare program (Figure 1). Rates of non-coverage decreased with increasing economic status, defined by income and family size, except for persons below the federally-defined poverty level, where the influence of another public program, the Medicaid program, is seen (Figure 2). Persons in families with incomes just above the federal poverty line (the "working poor") were least likely to be insured of any income group.

Some groups were found to be especially likely to lack insurance coverage (Figure 3). Virtually all minority groups exhibited non-coverage rates at least twice the rate found in the white, non-Hispanic population (8.0%). Persons of Hispanic origin appear to be especially poorly covered, followed by African-Americans. The practice of providing private health insurance as a benefit of employment among the working-age population is demonstrated by the high rates of non-coverage for respondents who were unemployed, temporarily laid off, or working only part-time. In contrast, both the permanently disabled (3.7% uninsured) and the temporarily disabled (7.9% uninsured) were found to be well insured relative to the general population.

Lack of health insurance can be a financial problem for individuals and can limit their access to needed preventive care and timely treatment. It

Figure 1. **Percent of Population without Health Insurance Coverage by Age Group, Rhode Island, 1990-1991.**



Submitted by the Office of Health Statistics, Jay S. Buechner, PhD, Chief. Health by Numbers *is edited by Jay S. Buechner, PhD, and William J. Waters, Jr, PhD.*

also impacts the health care system adversely. Although some groups with health care needs, such as the elderly, poor, and disabled, are well covered by public programs, the young adult population, which is at elevated risk for traumatic injuries, is most likely to lack coverage when needed. Also, there are many children in the state who lack coverage for needed preventive and screening services. These are the major gaps in the health care reimbursement system that require attention in order to reduce the overall rate of non-coverage in our population.

Figure 2. **Percent of Population without Health Insurance Coverage, by Family Economic Status, Rhode Island, 1990-1991.**

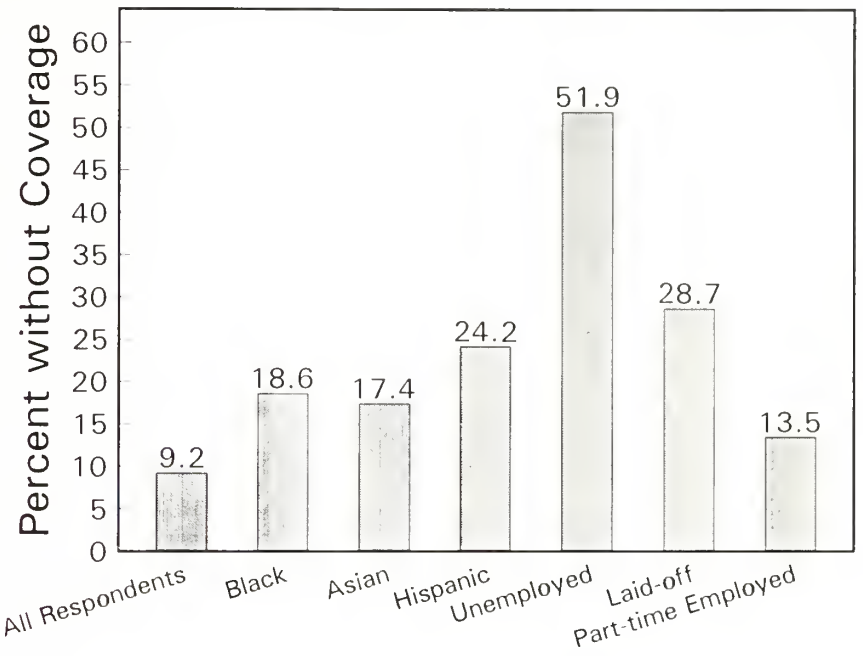
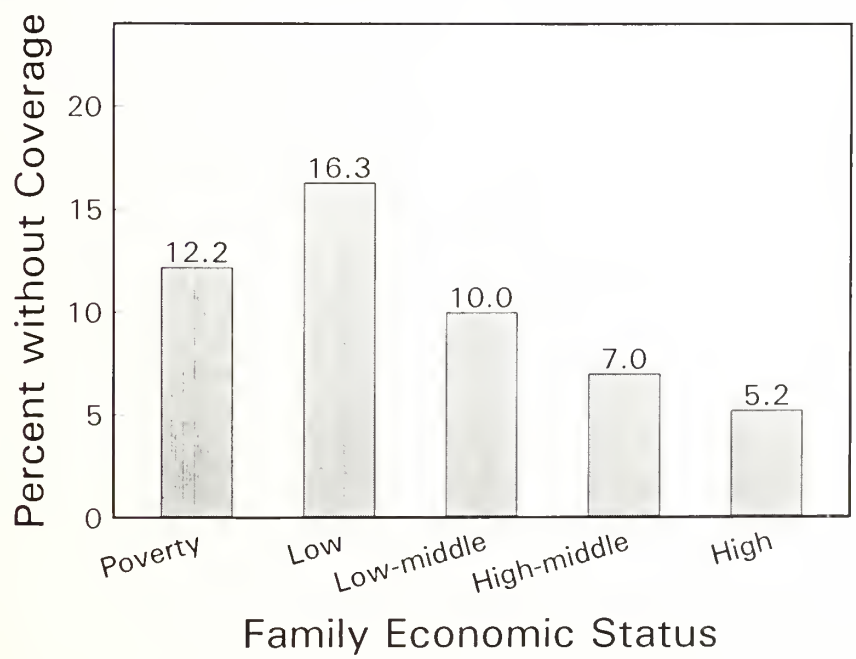


Figure 3. **Percent of Population without Health Insurance Coverage, Selected Groups, Rhode Island, 1990-1991.**



RECRUITING EMERGENCY PHYSICIANS

for new urgent care facility
in East Bay area.

Interest in Occupational Medicine required. Very attractive financial package including salary guarantee and prepaid malpractice insurance.

Please respond in writing to:

Box E
Rhode Island Medical Journal
106 Francis Street
Providence, RI 02903

OBGYN LIBRARY AVAILABLE

"Obstetrics/Gynecology"
1954-1991

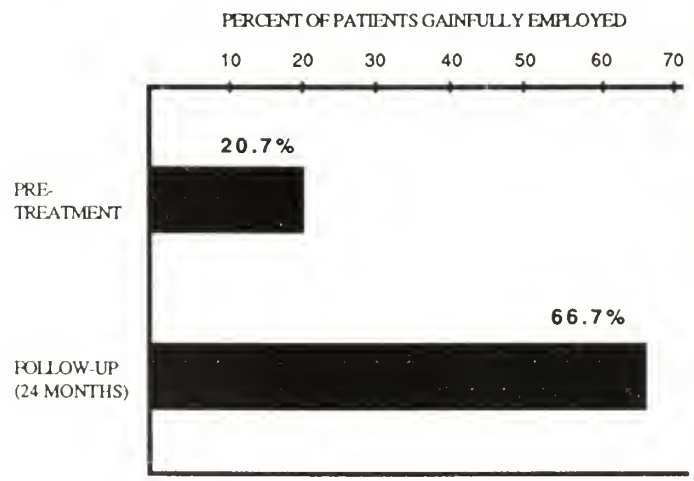
"American Journal of Obstetrics/Gynecology"
1951-1988

"Clinical Obstetrics and Gynecology"
1958-1988

"OBGYN Survey" - 1967-1990

For more information call
521-4471

"CHRONIC PAIN DOESN'T HAVE TO MEAN
CHRONIC DISABILITY FOR YOUR PATIENTS..."



The Chronic Pain Treatment Program
(401) 751-9150

Institute for Behavioral Medicine
120 Wayland Avenue
Providence, Rhode Island 02906-4318

THE RHODE ISLAND MEDICAL JOURNAL

The Official Organ of the Rhode Island Medical Society
Issued Monthly under the direction of the Publication Committee

VOLUME I
NUMBER 1

PROVIDENCE, R. I., JANUARY, 1917

PER YEAR $2.00
SINGLE COPY, 25 CENTS

THE RHODE ISLAND MEDICAL JOURNAL HERITAGE

Ninety Years Ago
(February, 1902)

Halsey DeWolf, MD describes the obstetrical experiences in the Providence Lying-In Hospital during the month of October, 1901. He notes that there were 26 admissions confined to the hospital, during this interval; of these, 18 cases were normal, full-term deliveries, one a miscarriage without complications, and the remaining seven, sufficiently abnormal to warrant description in the *Journal*. The first of these abnormal cases was a primipara with an abnormal transverse fetal presentation. With some difficulty, a podalic version was performed, yielding a dead fetus. A second case represented vomiting of pregnancy with renal complications. Treatment consisted of trophonine, malted milk and water. No mention of blood pressure. The third case was a woman in labor with an abscess of the uterine wall. The fourth case was a 24-year-old woman, pregnant six months, with albumen in her urine. Labor commenced and a dead fetus was delivered. Case five was a woman with interstitial nephritis who miscarried her pregnancy. Case six was an eclamptic woman seven months pregnant. She had leg edema, blurred vision, vomiting and convulsions. Labor was artificially begun and a living child delivered. Following delivery, the urinary output volume was greatly increased. Case seven represented a full-term delivery accompanied by shock and postpartum death, ascribed to an embolism from a uterine clot.

In a second article, Charles V. Chapin, MD, Superintendent of Health describes methods for the restriction of tuberculosis in Providence. The article points out that these measures must first be approved by the Board of Aldermen. First, he declares, tuberculosis should be placed on the list of notifiable diseases (which then included diphtheria and scarlet fever) and that both physicians and institutions be required to report. Health officers, when requested, will visit these cases. Numerous questions need to be answered. Ancestry, he points out, is not of so much importance as environment, in the etiology of tuberculosis. Secondly, we must devise means for the patient to take care of his sputum. Despite their frightening quality, Chapin recommends that circulars on sputum disposal be distributed to the public at large. To the poor, the City will distribute free paper cups for sputum collection. Chapin concludes: "It is to be hoped that some day there will be a hospital in the city for cases far advanced in phthisis. Disinfection of houses in which cases have lived is a good measure, but its importance is exaggerated. Washing with soap and water is as good a method as any. No effort to obtain a good milk supply can be successful, because no legislation can be obtained in Rhode Island towards securing a milk in this city which shall be free from the danger of tubercular infection."

To honor two famous scientist-professors at Brown University, the *Journal* publishes a poem composed by WW Bailey. The opening stanza:

Tonight two comrades we shall greet
Who come to us both laurel-crowned
And proud are we with them to meet,
Whose honors to us all redound.

The minutes of the quarterly meeting of the Rhode Island Medical Society are printed. Five new members are elected. The activities of the Providence Medical Society are also summarized including debates on the relative merits of surgery vs anti-cancer pastes in the treatment of lip cancer. Of special interest is a demonstration of the X-rays of two children with syphilis. The films showed enlargement of the tibiae.

Amongst the book reviews is a consideration of volumes III and IV (on Climatology) of the series, A System of Physiologic Therapeutics. The chapters include: Ocean Voyages; Mediterranean, European and British Health Resorts; Mineral Springs, Etc.

Fifty Years Ago
(February, 1942)

The entire issue is devoted to a single article, The Fiske Fund Prize

Essay, describing the surgical treatment of peptic ulcer, written by Adolph W. Eckstein, MD. The author notes that the past 30 years have seen a continuing strife between the internist and the surgeon regarding the appropriate treatment of peptic ulcer. There is agreement, though, that the patient with peptic ulcer is always a patient, the disease being recurrent and chronic; that he is never cured; that he must live at a diminished tempo, must eschew alcohol and tobacco, and must follow a careful diet in order to avoid recurrence of the ulcer. "Therefore, under proper dietary and habituary regime, successful, symptom-free patients might better be called controlled, than cured."

Eckstein reviews the various pathological studies of duodenal and gastric ulcers, and the rarer sites including the jejunal and acute anastomotic ulcers. After discussing the physiology of digestion and the pathophysiologic changes in peptic ulceration, he lists and elaborates upon the indications for surgery. He states ". . . it appears that the surgical treatment of an uncomplicated peptic ulcer is indicated only after all forms of medical treatment have been exhausted."

Five major indications for surgery are given: (1) Perforation, representing an acute abdominal, life-saving, emergency. The immediate surgical objective, here , is closure of the perforation, not surgical cure of the ulcer. (2) Pyloric obstruction, typically occurring only after years of chronic ulceration, with cicatricial stenosis of the pylorus. Retention, per se, is an inadequate reason for surgery. Only when retention persists despite medical treatment should surgery be considered. (3) Hemorrhage, next to perforation, the commonest cause of death in peptic ulceration. Some bleeding occurs in about 20 to 35% of all ulcers. In general, he states, "repetition of massive hemorrhage two or more times in patients under fifty years of age warrants surgical intervention as soon as the patient's general condition will permit an operation." (4) Failure of medical management. Such individuals who continue to have severe pain unrelieved by rest, diet and medication are proper candidates for surgery. And (5) Suspicion of cancer, particularly if the ulcer is gastric rather than duodenal, and if the ulcer crater exceeds 3 centimeters.

The author then summarizes the history of surgical interventions for ulcer, including such procedures as gastro-enterostomy, the various Billroth procedures, jejunal anastomoses, subtotal gastrectomy, and pyloroplasty.

He concludes: "The success of any operative procedure for peptic ulcer depends on many factors, most of which are under the control of the surgeon. Unsatisfactory results will occur, but no procedure is without risk nor does it insure one hundred percent relief from symptoms and complete protection from further trouble. To achieve the most in surgical treatment of duodenal and gastric ulcer, it is essential that the indications for operation be rigidly adhered to and that no operation be used as a routine procedure. Instead, the surgical procedure should be selected which most nearly meets the purpose of the intervention and which, after a thorough survey of the situation upon opening the abdomen, may be carried out with the maximum degree of safety."

Twenty-Five Years Ago
(February, 1967)

The lead article is by the eminent medical educator Lowell T. Coggeshal, MD, whose paper is entitled, New Directions in Medical Education. The author discusses the essentiality of teaching hospitals in training of medical students, notes changes in the direction of general practice in the United States, discusses the role of elementary education in the preparation of the modern medical student, talks about gradual revisions in the curricular schedules of contemporary medical schools and discusses the need for more trained physicians. He commends Brown University on its new and innovative program in medical education (leading to a master's degree in medical science), concluding: "Finally, let me urge you not to compromise, not to settle for harmless and harmonious mediocrity, and not to abandon the quest for new directions in medical education. Your success will bring ever increasing support from your community and will inspire others to dare follow along your path. My hat is off to those in this institution who deserve credit and great applause for creating such a wonderful instrument for the public welfare."

Florindo Simeone, MD, then Professor of Surgery at Western Reserve University, offers a paper on the new Brown University program in biomedical sciences, representing his speech given at the ground-breaking ceremonies (July 21, 1966) for the new Biomedical Complex at Brown. The talk emphasizes the need for medical schools to abolish the iron curtain between research in the fundamental sciences and applied medical art and science.

Francis Deitz, executive administrator of Memorial Hospital authors a paper on medical education in the community hospital. He concludes: "The community hospital is becoming an increasingly important cog in the medical education of the future. It needs assistance and leadership from the university teaching centers. In return it must live up to the responsibilities and standards that such an association demands."

Alfred L. Potter, MD, summarizes his experience with a happily married nurse whose first pregnancy required Cesarean section. In the subsequent 16 years, his patient underwent thirteen consecutive Cesarean sections. "She nursed all her babies. All are now living and well except one who died following an accident when two years old. None of these babies was premature."

Stanley D. Simon, MD describes sound principles for prepaid medical care noting that the providing of quality medical care cannot be dissociated from fair and reasonable payments for service.

This issue of the *Journal* presents scholarly book reviews by Robert V. Lewis, MD on texts describing the lives of Herman Boerhaave and John Morgan.

YOCON®
YOHIMBINE HCl

Description: Yohimbine is a 3a-15a-20B-17a-hydroxy Yohimbine-16a-carboxylic acid methyl ester. The alkaloid is found in Rubaceae and related trees. Also in Rauwolfia Serpentina (L) Benth. Yohimbine is an indolalkylamine alkaloid with chemical similarity to reserpine. It is a crystalline powder, odorless. Each compressed tablet contains (1/12 gr.) 5.4 mg of Yohimbine Hydrochloride.

Action: Yohimbine blocks presynaptic alpha-2 adrenergic receptors. Its action on peripheral blood vessels resembles that of reserpine, though it is weaker and of short duration. Yohimbine's peripheral autonomic nervous system effect is to increase parasympathetic (cholinergic) and decrease sympathetic (adrenergic) activity. It is to be noted that in male sexual performance, erection is linked to cholinergic activity and to alpha-2 adrenergic blockade which may theoretically result in increased penile inflow, decreased penile outflow or both.

Yohimbine exerts a stimulating action on the mood and may increase anxiety. Such actions have not been adequately studied or related to dosage although they appear to require high doses of the drug. Yohimbine has a mild anti-diuretic action, probably via stimulation of hypothalmic centers and release of posterior pituitary hormone.

Reportedly, Yohimbine exerts no significant influence on cardiac stimulation and other effects mediated by B-adrenergic receptors, its effect on blood pressure, if any, would be to lower it, however no adequate studies are at hand to quantitate this effect in terms of Yohimbine dosage.

Indications: Yocon® is indicated as a sympathicolytic and mydriatric. It may have activity as an aphrodisiac.

Contraindications: Renal diseases, and patient's sensitive to the drug. In view of the limited and inadequate information at hand, no precise tabulation can be offered of additional contraindications.

Warning: Generally, this drug is not proposed for use in females and certainly must not be used during pregnancy. Neither is this drug proposed for use in pediatric, geriatric or cardio-renal patients with gastric or duodenal ulcer history. Nor should it be used in conjunction with mood-modifying drugs such as antidepressants, or in psychiatric patients in general.

Adverse Reactions: Yohimbine readily penetrates the (CNS) and produces a complex pattern of responses in lower doses than required to produce peripheral a-adrenergic blockade. These include, anti-diuresis, a general picture of central excitation including elevation of blood pressure and heart rate, increased motor activity, irritability and tremor. Sweating, nausea and vomiting are common after parenteral administration of the drug.[1,2] Also dizziness, headache, skin flushing reported when used orally.[1,3]

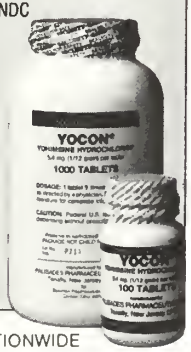
Dosage and Administration: Experimental dosage reported in treatment of erectile impotence.[1,3,4] 1 tablet (5.4 mg) 3 times a day, to adult males taken orally. Occasional side effects reported with this dosage are nausea, dizziness or nervousness. In the event of side effects dosage to be reduced to ½ tablet 3 times a day, followed by gradual increases to 1 tablet 3 times a day. Reported therapy not more than 10 weeks.[3]

How Supplied: Oral tablets of Yocon® 1/12 gr. 5.4 mg in bottles of 100's NDC 53159-001-01 and 1000's NDC 53159-001-10.

References:

1. A. Morales et al., New England Journal of Medicine: 1221, November 12, 1981.
2. Goodman, Gilman — The Pharmacological basis of Therapeutics 6th ed., p. 176-188. McMillan December Rev. 1/85.
3. Weekly Urological Clinical letter, 27:2, July 4, 1983.
4. A. Morales et al., The Journal of Urology 128: 45-47, 1982.

Rev. 1/85



AVAILABLE AT PHARMACIES NATIONWIDE

PALISADES PHARMACEUTICALS, INC.
219 County Road
Tenafly, New Jersey 07670
(201) 569-8502
1-800-237-9083

INFORMATION FOR AUTHORS

Manuscripts: Manuscripts will be accepted for consideration with the understanding that they are original contributions, have never been published or submitted elsewhere, and are submitted only to the *Rhode Island Medical Journal*.

Specifications: Manuscripts must be original typed copy (not all capitals) on 8-1/2 x 11 inch firm typewritten paper, double-spaced throughout (including title page, text, acknowledgments, and references) with margins of at least one inch and using but one side of each page. Tables, charts, and legends should be submitted separately from the text, and referred to by number (ie, Fig. 1) within the text. Subheadings must be inserted at reasonable intervals to break the typographic monotony of the text. Pages must be numbered consecutively. Italics and boldface print are never used except as subheadings.

Abbreviations: The *Journal* attempts to avoid the use of jargon and abbreviations. All abbreviations, especially of laboratory and diagnostic procedures, must be identified in the text.

Title Page: All manuscripts must include a title page which provides the following information: (1) a concise and informative title; (2) the name of the author or authors with their highest academic degree (ie, MD, PhD); (3) a concise biographical description for each author which includes specialty, practice location, academic appointment, and primary hospital affiliation; (4) mailing address and office telephone of principal author; (5) mailing address of author responsible for correspondence or reprint requests; (6) source of support if applicable.

Illustrations: Authors are urged to use the services of professional illustrators and photographers. Drawings and charts should always be done in black ink on white paper. Clear, black and white 5x 7 glossy photographs should be submitted, and such illustrations numbered consecutively and their positions indicated in the text. Original magnifications should be noted. Illustrations defaced by handwriting or excessive handling will not be accepted. The figure number, indication of the top, and the name of the author must be attached to the back of each illustration. Legends for illustrations should be typewritten on a single list, with the numbers corresponding to those on photographs and drawings. Recognizable photographs of patients are to be appropriately masked and must carry with them written permission for publication. Special arrangements must be made with the editors for excessive numbers of illustrations. Color plates are not acceptable.

Identification of Patients: Names, initials should not be used. Use of numbers is a preferable form of identification.

Reprints: Because of cost considerations, reprints are not provided routinely to the author(s). Reprints may be ordered separately (100 copies minimum order) and printing costs will be charged to the author(s).

Responsibility: Manuscripts are subject to editorial revisions as deemed necessary by the editors and such modifications will be undertaken so as to bring them into conformity with *Journal* style, which is in compliance with the editorial standards of the AMA. However, neither the editors, nor the publishers, nor the Rhode Island Medical Society will accept responsibility for statements made or opinions expressed by any contributors in any article or feature published in the pages of the *Journal*.

Permission: When material is reproduced from other sources, full credit must be given both to the author and publisher of these sources. Where work is reported from a governmental service or institution, clearance by the appropriate authority must accompany the manuscript.

References: To conserve space and expense, references should be limited to those essential to the subject. The editor reserves the right to reduce the number when it is deemed necessary. The references must be double-spaced and numbered as they appear consecutively in the text, with their positions clearly indicated in the text. All references must be checked to assure complete accuracy. Each journal reference must include the full name of the author(s); complete title of paper; name of publication; volume number; issue number; first and last page of paper; and date (year, month, and day as indicated). Each book reference must include the full name of author(s), editor(s), or both, with initials; title of book; edition; publisher; location; year of publication, volume (if given); and page number. If the reference is to a chapter within a book, the author of the chapter, if different than the author of the book, and the title of the chapter (if any) must be provided.

Correspondence: All correspondence relating to publication should be addressed to: Managing Editor, *Rhode Island Medical Journal*, 106 Francis Street, Providence, RI 02903.

ONCE DAILY 180mg Calan SR verapamil HCl SUSTAINED-RELEASE CAPLETS

The recommended starting dose for Calan SR is 180 mg once daily. Dose titration will be required in some patients to achieve blood pressure control.

A lower initial starting dosage of 120 mg/day may be warranted in some patients (eg, the elderly, patients of small stature)

Constipation, which is easily managed in most patients, is the most commonly reported side effect of Calan SR

BRIEF SUMMARY

Contraindications: Severe LV dysfunction (see *Warnings*), hypotension (systolic pressure < 90 mm Hg) or cardiogenic shock, sick sinus syndrome (if no pacemaker is present), 2nd- or 3rd-degree AV block (if no pacemaker is present), atrial flutter/fibrillation with an accessory bypass tract (eg, WPW or LGL syndromes), hypersensitivity to verapamil.

Warnings: Verapamil should be avoided in patients with severe LV dysfunction (eg, ejection fraction < 30%) or moderate to severe symptoms of cardiac failure and in patients with any degree of ventricular dysfunction if they are receiving a beta-blocker. Control milder heart failure with optimum digitalization and/or diuretics before Calan SR is used. Verapamil may occasionally produce hypotension. Elevations of liver enzymes have been reported. Several cases have been demonstrated to be produced by verapamil. Periodic monitoring of liver function in patients on verapamil is prudent. Some patients with paroxysmal and/or chronic atrial flutter/fibrillation and an accessory AV pathway (eg, WPW or LGL syndromes) have developed an increased antegrade conduction across the accessory pathway bypassing the AV node, producing a very rapid ventricular response or ventricular fibrillation after receiving I.V. verapamil (or digitalis). Because of this risk, oral verapamil is contraindicated in such patients. AV block may occur (2nd- and 3rd-degree, 0.8%). Development of marked 1st-degree block or progression to 2nd- or 3rd-degree block requires reduction in dosage or, rarely, discontinuation and institution of appropriate therapy. Sinus bradycardia, 2nd-degree AV block, sinus arrest, pulmonary edema and/or severe hypotension were seen in some critically ill patients with hypertrophic cardiomyopathy who were treated with verapamil.

Precautions: Verapamil should be given cautiously to patients with impaired hepatic function (in severe dysfunction use about 30% of the normal dose) or impaired renal function, and patients should be monitored for abnormal prolongation of the PR interval or other signs of overdosage. Verapamil may decrease neuromuscular transmission in patients with Duchenne's muscular dystrophy and may prolong recovery from the neuromuscular blocking agent vecuronium. It may be necessary to decrease verapamil dosage in patients with attenuated neuromuscular transmission. Combined therapy with beta-adrenergic blockers and verapamil may result in additive negative effects on heart rate, atrioventricular conduction and/or cardiac contractility; there have been reports of excessive bradycardia and AV block, including complete heart block. The risks of such combined therapy may outweigh the benefits. The combination should be used only with caution and close monitoring. Decreased metoprolol and propranolol clearance may occur when either drug is administered concomitantly with verapamil. A variable effect has been seen with combined use of atenolol. Chronic verapamil treatment can increase serum digoxin levels by 50% to 75% during the first week of therapy, which can result in digitalis toxicity. In patients with hepatic cirrhosis, verapamil may reduce total body clearance and extrarenal clearance of digitoxin. The digoxin dose should be reduced when verapamil is given, and the patient carefully monitored. Verapamil will usually have an additive effect in patients receiving blood-pressure-lowering agents. Disopyramide should not be given within 48 hours before or 24 hours after verapamil administration. Concomitant use of flecainide and verapamil may have additive effects on myocardial contractility, AV conduction, and repolarization. Combined verapamil and quinidine therapy in patients with hypertrophic cardiomyopathy should be avoided, since significant hypotension may result. Concomitant use of lithium and verapamil may result in a lowering of serum lithium levels or increased sensitivity to lithium. Patients receiving both drugs must be monitored carefully. Verapamil may increase carbamazepine concentrations during combined use. Rifampin may reduce verapamil bioavailability. Phenobarbital may increase verapamil clearance. Verapamil may increase serum levels of cyclosporin. Verapamil may inhibit the clearance and increase the plasma levels of theophylline. Concomitant use of inhalation anesthetics and calcium antagonists needs careful titration to avoid excessive cardiovascular depression. Verapamil may potentiate the activity of neuromuscular blocking agents (curare-like and depolarizing); dosage reduction may be required. There was no evidence of a carcinogenic potential of verapamil administered to rats for 2 years. A study in rats did not suggest a tumorigenic potential, and verapamil was not mutagenic in the Ames test. Pregnancy Category C. There are no adequate and well-controlled studies in pregnant women. This drug should be used during pregnancy, labor, and delivery only if clearly needed. Verapamil is excreted in breast milk, therefore, nursing should be discontinued during verapamil use.

Adverse Reactions: Constipation (7.3%), dizziness (3.3%), nausea (2.7%), hypotension (2.5%), headache (2.2%), edema (1.9%), CHF, pulmonary edema (1.8%), fatigue (1.7%), dyspnea (1.4%), bradycardia HR < 50/min (1.4%), AV block total 1°,2°,3° (1.2%), 2° and 3° (0.8%), rash (1.2%), flushing (0.6%), elevated liver enzymes, reversible non-obstructive paralytic ileus. The following reactions, reported in 1.0% or less of patients, occurred under conditions where a causal relationship is uncertain: angina pectoris, atrioventricular dissociation, chest pain, claudication, myocardial infarction, palpitations, purpura (vasculitis), syncope, diarrhea, dry mouth, gastrointestinal distress, gingival hyperplasia, ecchymosis or bruising, cerebrovascular accident, confusion, equilibrium disorders, insomnia, muscle cramps, paresthesia, psychotic symptoms, shakiness, somnolence, arthralgia and rash, exanthema, hair loss, hyperkeratosis, macules, sweating, urticaria, Stevens-Johnson syndrome, erythema multiforme, blurred vision, gynecomastia, galactorrhea/hyperprolactinemia, increased urination, spotty menstruation, impotence.

4/11/91 • P91CA6277V

Address medical inquiries to
G.D. Searle & Co.
Medical & Scientific
Information Department
4901 Searle Parkway
Skokie, IL 60077

SEARLE G.D. Searle & Co. Box 5110, Chicago, IL 60680

A91CA6148T

ONCE DAILY 180mg
Calan SR
verapamil HCl
SUSTAINED-RELEASE CAPLETS
A MILD START IN MILD HYPERTENSION
When diet and exercise alone are not enough...
© 1991 G.D. Searle & Co.

RHODE ISLAND MEDICINE

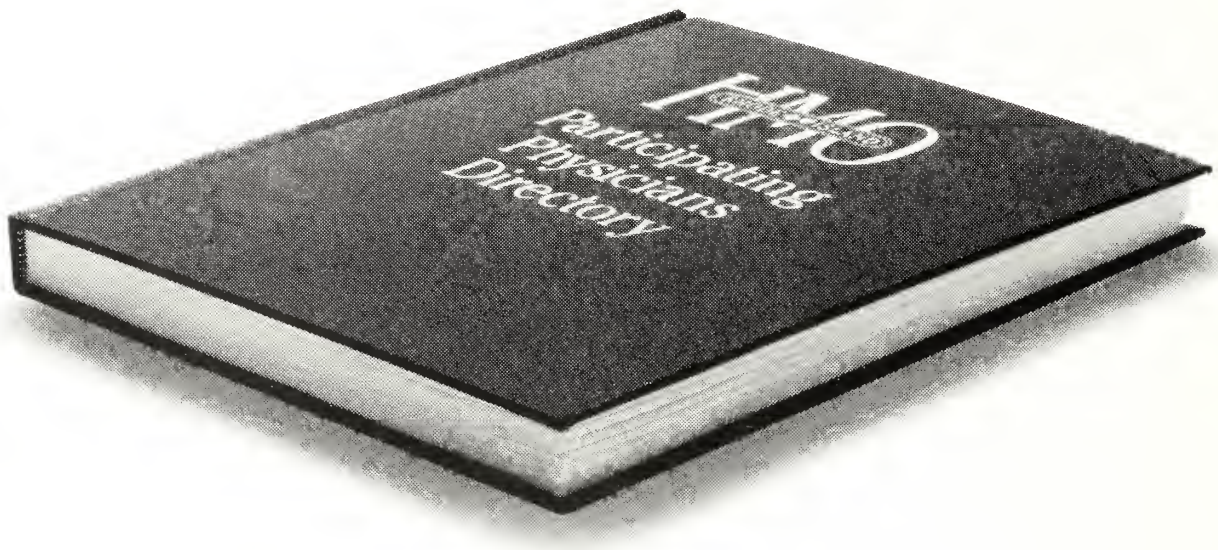
March 1992

Volume 75, Number 3

Ethical Issues in Medicine

FRANCIS A COUNTWAY LIB OF MED
EXCHANGE OFFICE
10 CHATTUCK STREET
BOSTON MA 02115

This book has a happy ending.



And a happy beginning. And a happy middle.

That's no fiction. It's because we re-wrote the book on provider relations. With higher office visit allowances than other major plans. And with quick, easy access to both our Medical Director and Provider Relations staff.

But while we could cover all the reasons we're sure you'd like HMO Rhode Island, we think the best way to judge this book is to hear about it from our Primary Care Physicians and Specialists, themselves.

So ask your colleagues for the real story. Then call Physician Recruitment Manager, Carin Cookman, at (401)274-6674, or 1-800-528-4141. Or take her call when it comes.

HMO RHODE ISLAND

The Ultimate Health Maintenance Organization.

RHODE ISLAND MEDICINE

EDITORIAL STAFF

Stanley M. Aronson, MD
Editor-in-Chief

Kimberly A. Poulton
Managing Editor

Hugo Taussig, MD
Book Review Editor

Seebert J. Goldowsky, MD
Editor-in-Chief Emeritus

EDITORIAL BOARD

*Edward R. Feller, MD
Chairman

*Joseph Amaral, MD

*Stanley M. Aronson, MD

Edward M. Beiser, PhD, JD

Paul Calabresi, MD

*Richard A. Carleton, MD

Margaret Coloian, MSJ

*James P. Crowley, MD

*Peter A. Hollmann, MD

*Margaret A. Neill, MD

*Frank J. Schaberg, Jr., MD

*Fred J. Schiffman, MD

William J. Waters, Jr., PhD

*Member of Publications Committee

OFFICERS

Kathleen C. Hittner, MD
President

Robert E. Baute, MD
President-Elect

A. Robert Buonanno, MD
Secretary

Frances P. Conklin, MD
Treasurer

Richard Wong, MD
Immediate Past President

DISTRICT AND COUNTY PRESIDENTS

Fred Vohr, MD
Bristol County Medical Society

William F. Coscina, MD
Kent County Medical Society

Orest Zaklynsky, MD
Newport County Medical Society

David P. Carter, MD
Pawtucket Medical Association

James P. Crowley, MD
Providence Medical Association

Joseph R. Dotolo, MD
Washington County Medical Society

Patrick R. Levesque, MD
Woonsocket District Medical Society

Volume 75, Number 3 March 1992

TABLE OF CONTENTS

COMMENTARIES

119 Choice and Dilemma

The Physician Who Collected Words

The Language of Epidemiology (IX.) Risk

CONTRIBUTIONS

Ethical Issues in Medicine

123 **The Rights of the Terminally Ill and Physician-Assisted Suicide**
Barbara A. DeBuono, MD, MPH

127 **The Hospice Response to Proposals of Assisted Suicide**
David Rehm, ACSW
Edward Martin, MD

129 **Physician-Assisted Suicide: A Battle of Technology and Morality**
David A. Ames, D. Min.

133 **The Ethics of Research in Incurable Disease**
Lester S. Adelman, MD

136 **Ethical Dilemmas in America's Health Care System**
Aging 2000 Staff

145 **The Recent Controversy over Breast Implants and Their Risk**
Howard S. Sturim, MD, FACS

147 **Suicide in Newport County 1975-1989**
William F. Hoffmann, MD

157 **Doctors, Drug Companies and Gifts: Some Local Views**

COLUMNS

152 **HEALTH BY NUMBERS**
Elder Suicide in Rhode Island

163 **THE RHODE ISLAND MEDICAL JOURNAL HERITAGE**

Cover: "Study of a Figure with Arm Outstretched" by Anthony Van Dyck. From the Museum of Art, Rhode Island School of Design. Gift of Mrs. Gustav Radeke.

Rhode Island Medicine is owned and published monthly by the Rhode Island Medical Society, 106 Francis Street, Providence, Rhode Island 02903, Ph 401-331-3207 Single copies $2 00 — Subscriptions $20 00 per year (members of the Rhode Island Medical Society — $5 00 annually). Published articles represent opinions of the authors and do not necessarily reflect the official policy of the Rhode Island Medical Society unless clearly specified. Advertisements do not imply sponsorship or endorsement by the Rhode Island Medical Society Second class postage paid at Providence, Rhode Island ISSN 0363-7913 POSTMASTER Send address changes to RHODE ISLAND MEDICINE, 106 Francis Street, Providence, RI 02903 National Advertising Bureau State Medical Journal Advertising Bureau, Inc , 711 South Blvd , Oak Park, Illinois 60302. Phone 708-383-8800.

QUESTION:

WHAT ARE THE THREE MOST IMPORTANT THINGS TO CONSIDER WHEN CHOOSING AN INSURANCE AGENCY?

ANSWER:

EXPERIENCE, EXPERIENCE, EXPERIENCE

INSURANCE SINCE 1879

STARKWEATHER & SHEPLEY INC. - (401) 421-6900

Morton Smith, Inc. - (401) 861-6800

155 South Main Street
Providence, Rhode Island 02903

COMMENTARIES

Choice and Dilemma

Why does it appear that the number of ethical problems confronting today's physician is increasing? Did our professional predecessors face similar problems but manage them with greater equanimity, in relative silence, and without interminable symposia, monographs and handwringings? Six decades ago, there were no periodicals devoted to biomedical ethics; today in the English speaking world alone, there are more than 220 such journals. There is scarcely a US medical school without a few courses in ethics and many of the more affluent schools maintain independent, financially secure departments of biomedical and social ethics. It appears that medical ethics has now assumed the dimension of a growth industry.

A second question: The human condition has not changed materially, yet each recent decade carries its own novel agenda of ethical problems. Why this rapid evolution in the nature of moral dilemmas?

The answer to both questions may be found in the domain of choice. When your cupboard stores only bread and porridge, no culinary dilemmas arise; but let there be many varieties of foods available and intolerable problems of choice will surely emerge.

Six decades ago, the great majority of deaths took place in the home unattended by any life-prolonging measures. Resuscitation was something reserved for the nearly-drowned and oxygen was a chemical element with little assigned role in medicine. Organ transplants were confined to a new literary genre called science fiction; triage was a word known only to the military. Death in those days could be predicted but was neither denied nor delayed. Where there was no meaningful intervention, no choice existed; and with no choice, of course, no realistic ethical questions arose. Choice, like Promethean freedom, brings its special burden of problems.

Medical ethics, "the systematic study of human conduct in the area of life sciences and health care in the light of moral values and principles" assumes great importance only when we confront choice. Issues never encountered in the medicine of six decades ago now include: the public fear of expanding medical technologies; the limits of informed consent; genetic engineering; the inevitable tensions between patient and physician (physician's judgment vs the patient's autonomy); the assignment of scarce transplantable organs; and the limits to the privacy demands of the patient (the airlines pilot with a brain tumor).

Increasingly, the papers submitted to *Rhode Island Medicine* address the ethical problems coloring the practice of modern medicine. They reflect the increasing concerns experienced by physicians and others in the moral implications of health care alternatives. This issue prints a number of these papers.

Stanley M. Aronson, MD

The Physician Who Collected Words

English, the richest of all languages, has borrowed unabashedly from its many lingual forebears. Celtic, Latin, Greek, Old German, Saxon and other Teutonic tongues, Danish and Norman French each lay claim to a measure of authorship since each, in sequence, had impressed itself upon what was initially a primitive and insular language. Current English, now the most accretive of languages, has no single mother tongue. To this day, it continues shamelessly to absorb the vernacular flavor of many interacting languages; the formal English dictionary contains more entries than the dictionaries of any other language: more borrowings; more synonyms; more lusty, subtle variants; more ways of saying things, of offering texture to objects and ideas than any other tongue.

An evolving language is an exciting, yet disquieting, thing because it rarely allows for strict formalization. It wasn't until the 18th and 19th centuries, with the publication of the great Johnson and Webster dictionaries and similar texts, that English became somewhat regularized in spelling and grammar. A novel way of arranging words, a new form of dictionary – offering clusters of synonyms and antonyms rather than definitions – was first proposed and assembled in the mid-19th century through the avocational enterprise of a London physician, Peter Mark Roget. His text, now modified by over 100 subsequent editions, survives today as *Roget's Thesaurus*.

Roget's father was a Calvinist pastor in Geneva who assumed the pulpit of the French Church in London during the reign of George III. He married an English woman, became a permanent resident of London and fathered but one child, Peter Mark, born on January 18, 1779. This son, as a child, showed great intellectual aptitude and

an early interest in medicine. He completed, with distinction, his medical studies at the University of Edinburgh and then travelled extensively through Europe before establishing his medical practice in Manchester, England. In 1804, Roget was appointed a physician to the Manchester Infirmary and while there was one of the faculty founders of the University of Manchester School of Medicine. His fame as an internist and experimental physiologist brought him to London in 1808 where he helped to found the great Northern Dispensary. He joined the faculty of the University of London becoming its first Fullerian Professor of Physiology. During this time he maintained a thriving private practice.

Roget's medical publications included a two-volume text on animal and vegetable physiology (1834, first American edition, 1839), a two-volume text on physiology and phrenology (1838), and numerous books on the medical aspects of electricity, galvanism, magnetism and electromagnetism. He contributed many papers to the leading medical and biological journals of his era, on subjects as varied as aging, asphyxia and communication systems for the deaf and dumb. In 1815 he was elected to the Royal Society, becoming its Secretary in 1821.

Roget retired from his professorship, as well as from his private practice, in 1849, at the age of 61. As a means of filling his time after retirement, he invested his energies in the pursuit of applied mathematics (inventing the log-log slide rule) and in the creation of a new form of word collection based upon cross-referenced lists of synonyms and antonyms. In 1852, after 13 years of intense and absorbing labor, he submitted his specialized dictionary for publication. Its original title was: "*Thesaurus of English Words and Phrases Classified and Arranged so as to Facilitate the Expression of Ideas and Assist in Literary Composition.*" Despite this lengthy, burdensome title, the text achieved immense and virtually instant success. A new edition was assembled in 1853; yet another modified edition in 1855, and for the next few decades, a new and expanded edition appeared at yearly intervals. The first American edition, printed in Boston, appeared in 1854. A French counterpart, Robertson's *Dictionaire Ideologique*, was published in Paris, 1859.

The wide literary and material success of the Thesaurus was such that both of Roget's sons devoted their energies to this project for many decades following the death of their father on September 12, 1869.

Roget chose the word thesaurus to define his work although he was not the first to employ this term to describe a dictionary. In 1565, Cooper had authored a text entitled, *Thesaurus Linguae Romanae et Britannicae*. The word thesaurus is derived from the Greek *thesauros*, meaning a treasury or storehouse. A cognate word in medicine, thesaurismosis, assumes a more somber meaning: namely a metabolic storage disease (such as Tay-Sachs and Gaucher's diseases.)

Roget, an experimental physiologist, a consulting internist of great repute, a founder of an outstanding British medical school, and a mathematician of some note, also aided those struggling with the English language. For persons seeking that unique word so as to convey a thought with greater force, precision and clarity, he devised a novel mechanism for quick access to the expanding treasury of English words. Roget was one of a measured number of scientists capable of unique achievement in more than one field of endeavor. They seldom make such people any more.

Stanley M. Aronson, MD

The Language of Epidemiology (IX). Risk

Risk is defined as the numeric probability of an untoward outcome. Risk varies from 0.0 (absolute certainty that the outcome will not materialize) to 1.0 (absolute certainty that it will). In the real world of course, where certainties are seldom encountered, risk values tend to lie between the two numeric extremes. Thus, for example, we say that the risk of rain tomorrow is 0.3 (3 chances in 10). By convention, risk describes only the likelihood of unpleasant events (disease, inclement weather, economic recession, etc.). It would be bizarre, for example, to talk of the risk of balmy weather.

The numeric value assigned to a specific risk is based upon our past experience with those prior circumstances (exposures) identified with each outcome. For example, we know, in recent years, that 0.56 persons per 1,000, each year, will develop lung cancer (risk = 0.00056). In the subpopulation of those who smoke heavily, however, the risk rises to 0.0096 (a 17-fold increase in risk). When we say that an individual, Mr Z, during the next year will face a 0.0096 risk of lung cancer, we are really saying that in a population of heavily smoking males reasonably similar to Mr Z, about 9.6 persons per 1,000 (approximately 1 in 100) will have developed lung cancer within a 12 month interval. Risk, although applied to individuals, nevertheless represents the collective experience in populations defined by certain tangible characteristics. Risk, which attempts to predict the likelihood of a perverse outcome during a specified time interval, is also necessarily a time-dependent measure.

Risk, then, is a gauge of our knowledge, such as it is, of the causal factors (called risk factors) leading to a particular disease. And to the extent that the expression of risk is other than 0.0 or 1.0, risk is also a measure of our ignorance of these many, as yet unidentified, contributory forces, some genetic and some environmental. If we truly knew all the etiologic factors and cofactors which determine a particular disease, we could then identify with certainty those who in the future will or will not develop the studied disease.

To illustrate how expanding knowledge leads to risk probabilities approaching one numerical extreme or another, consider the following hypothetical happening:

An alien arrives from a distant planet to observe earthlings. The alien notes that an occasional earthling will generate (give birth to) a new earth-

ling. The alien views this generative event as an ill-defined threat; and as such he documents its occurrence in quantitative terms of risk.

In his initial studies of earthlings, the alien has yet to appreciate the distinction between male or female, young or old, and those living as couples or those alone. In his first report to his home planet, therefore, he indicates that the number of completed pregnancies is about 15 per 1,000 earthlings per year (risk = 0.015). Only after prolonged observation does the alien perceive that a sub-population of earthlings (called males) generate no babies (risk = 0.0). Similarly, pregnancy is virtually unknown in the other major category of earthlings (called females) who are younger than 16 or older than 50 years. His second report then indicates that the risk of pregnancy in the female subpopulation between ages 15 and 50 years is 0.09.

In subsequent reports to his home office, after learning of still other variables which modify the probability of pregnancy (marriage, use of contraceptives, conscious intent to become pregnant, gynecologic health, fertility of male partner, etc.) the alien now states with developing certainty which earthlings will not give birth (all males; and certain females defined by measurable characteristics) and which will. Indeed, in certain carefully defined sub-populations, the alien can assign a pregnancy-risk value in excess of 0.8. Thus, from an initially intermediate risk level, the alien was able to drive the risk probabilities in carefully portrayed subpopulations in either direction to 0.0 or 1.0.

The greater our knowledge of the operative risk factors which either predispose or prevent a specified outcome, the greater will the likelihood be that our assigned numeric risks will approach either of the two probability extremes of absolutely yes or no. With total knowledge, an unlikely happenstance, we should then be able to state categorically that any studied individual either will or will not eventually be victim to an explicit disease. In very rare autosomal recessive diseases this is already a reality.

Stanley M. Aronson, MD

April, 1992
Contents

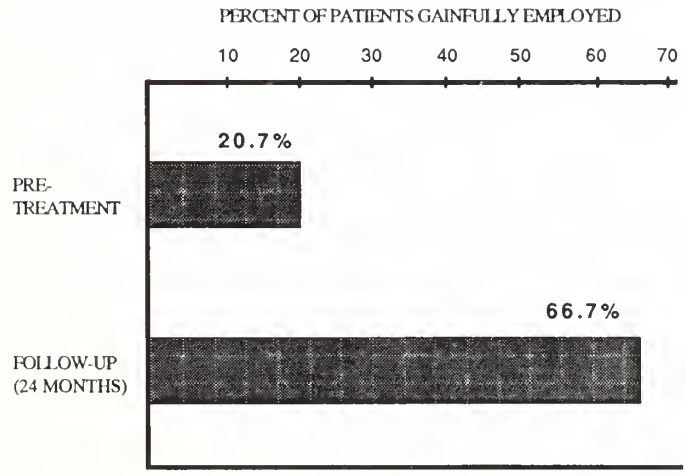
RHODE ISLAND MEDICINE

Schistosomiasis

Guest Editors:
G. Richard Olds, MD
Paul M. Knopf, PhD

THE FRANCIS A. COUNTWAY
LIBRARY OF MEDICINE
BOSTON, MA
MAR 10 1992

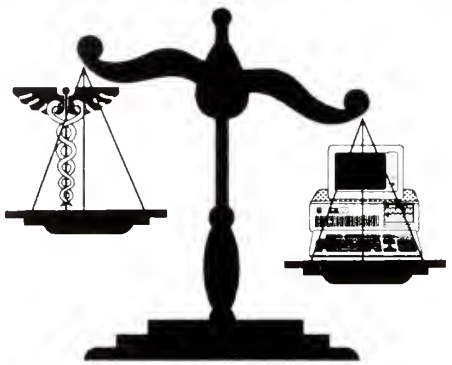
"CHRONIC PAIN DOESN'T HAVE TO MEAN CHRONIC DISABILITY FOR YOUR PATIENTS..."



The Chronic Pain Treatment Program
(401) 751-9150

Institute for Behavioral Medicine
120 Wayland Avenue
Providence, Rhode Island 02906-4318

BALANCE THE MEDICAL SIDE OF YOUR PRACTICE WITH THE BUSINESS SIDE



Vanguard Medical Management Services gives you and your staff more time for the medical side of your practice.

You love medicine. You and your staff are devoted to providing the best patient care possible. But, the business side of your medical practice is becoming more and more demanding. Frequent and complicated changes in medical insurance claims processing and accounting procedures are pulling your office staff away from medical and patient care services over to the business side of your practice. Maybe it's time to add a medical management service to your practice.

Vanguard Medical Management Services offers a comprehensive practice management service designed to free you and your office staff from time-consuming accounting and claims processing chores, plus provides qualified office staff for short, long-term and permanent assignments. Our team of experienced professionals help you and your staff manage the business side of your practice more efficiently, giving you more time to devote to your patients. You can trust us to provide:

- ✔ *Guaranteed revenue maximization*
- ✔ *Fast, accurate electronic claims processing for commercial insurance carriers, Blue Shield, HMOs, Medicare and Medicaid.*
- ✔ *A knowledgeable service representative dedicated to your practice*
- ✔ *Professional accounting/payroll services*
- ✔ *A confidential evaluation of your fee schedules*
- ✔ *Permanent and temporary staffing services*
- ✔ *Courteous, understanding and helpful response to your patients' billing questions.*

Call Geri Matraia at **(508) 842-4947** or **1(800) 743-2888** for information about putting **Vanguard Medical Management Services** to work for your practice.
New client consultations are free.

512 West Main Street, Shrewsbury, MA 01545

The Rights of the Terminally Ill and Physician-Assisted Suicide

Barbara A. DeBuono, MD, MPH

The principle of beneficence . . . requires that a physician should assist in making a patient's death as painless as possible.

It is essential that the issue of how an individual is permitted to manage his or her death be openly discussed if medicine as a profession hopes to restore the compassion and sensitivity that many feel has been lost in this era of widespread high-tech health care. The debate needs to take place in Rhode Island, as it has in Washington State, California, and other places. As the debate is advanced, society must be prepared for the pain and anxiety that it will generate.

This paper will review the principle of *beneficence* – performance of acts that are kind and charitable based upon the principle of respect of the autonomy of the patient, then move on to *advance directives*, and close with a discussion of *physician-assisted suicide*.

Beneficence

Proponents of euthanasia and physician-assisted suicide claim that the principle of beneficence: performance of kind, charitable acts which are conducive to personal well being, should drive the medical profession and society to enhance patients' autonomy in managing their own death. To expand further, the principle holds that such respect of patients' autonomy would allow them to choose the manner of their death. The principle of beneficence further requires that a physician should assist in making a patient's death as painless as possible. In the Cruzan case, this would include withholding treatment. "A patient has the right to refuse treatment, even if such a refusal will bring about the patient's death."[1]

Barbara A. DeBuono, MD, MPH, is Director of Health, RI Department of Health, Providence, Rhode Island.

Advance Directives

Many states have laws that recognize advance directives in which a patient can express in writing his or her treatment preference in the event of a serious, life-threatening condition. Living Will statutes date back 15 years. However, only 8 to 15% of American adults have prepared a living will.[2] The Patient Self-Determination Act passed by Congress last year requires that, as of 1 December 1991, health care facilities that are Medicare and Medicaid certified must inform patients about their right to prepare advance directives. The law now forces the issue on practitioners and patients. Advance Directives are formalized, written means for conveying instructions of health care. Rhode Island has two types of advance directives: 1) The Durable Power of Attorney for Health Care, and 2) The Living Will. This state has had the Durable Power of Attorney for Health Care since 1987, and a Living Will since 1991. Briefly, the difference between the two is the following:

a) A *Living Will* permits people older than 18 to specify in writing that they want medical care withheld or withdrawn if they are terminally ill and unable to communicate. The declaration will take effect provided the attending physician knows about it, determines the condition is terminal, and the patient is unable to make decisions.
b) The *Durable Power of Attorney for Health Care* allows people older than 18 to designate someone to make health care decisions for them if they become incapacitated.

It's best to have both documents completed because there may be

ABBREVIATIONS USED:
ACP: American College of Physicians
HARI: Hospital Association of Rhode Island

medical circumstances that arise which are not covered by the Living Will.

Staff of the Department of Health, along with the Departments of Elderly Affairs and Human Services, have worked with the Hospital Association of Rhode Island (HARI) to prepare documents and educational materials to be used in this endeavor. The Department of Health has printed 10,000 copies of the Living Will and Durable Power of Attorney for Health Care; HARI has printed an instructional booklet entitled "Making Your Health Care Decisions: It's Up To You." Distribution of materials will be through state libraries, the Health Department's Division of Vital Records, senior centers, hospitals, and nursing homes. The people who need this information include patients of hospitals, nursing homes, and most importantly, the general public.

The key to the utility of advance directives is to have the documents prepared before the individual becomes acutely or terminally ill.

The key to the utility of advance directives is to have the documents prepared before the individual becomes acutely or terminally ill. In the case of a sudden, debilitating accident, it is clearly advantageous to have the patient's wishes defined and specified before such questions arise. This spares families terrible anguish and discord, and prevents needless hospital and medical expenditures.

The Patient Self-Determination Act now obligates health care providers and institutions to obtain patients' preferences regarding medical interventions at times when their lives hang in the balance. The Act forces providers and patients to openly confront this difficult issue. There are potential uncertainties, however, as outlined in a recent study of dialysis patients who suggested that they were not entirely sure how strictly they wanted their advance directives followed.[3]

Advance directives constitute one end of the spectrum of patient self-determination. It is a meaningful, humane, rational approach that legally allows an individual to have a tremendous amount of control in the determination of the manner of his or her own death. The other end of the advance directive spectrum is physician-assisted suicide: where the patient seeks the assistance of a physician in taking his or her own life – the ultimate act of self-determination.

Physician-Assisted Suicide

Physicians have had a long tradition of allowing patients to die. Pneumonia is said to be the "old man's friend" because it commonly occurs in elderly patients with strokes or other debilitating illnesses and, if untreated, allows the patient to die in a few days. Once the decision is made to let a patient die however, it can be argued that the physician must make the death as swift and painless as possible.[4]

Killing Patients vs Allowing Them to Die

Some philosophers have rejected the distinction that maintains that it is morally acceptable to allow terminally ill patients to die, but unacceptable to kill them directly. They say it is no different to terminate dialysis and let a person without kidneys die a slow insidious death from uremia, than it is to give them a lethal injection of a barbiturate.

The distinction between killing patients and allowing them to die is a serious one, and will continue to be debated by ethicists.

Recent Examples

The role of physicians in euthanasia and assisted suicides was rekindled by the death in June, 1990 of Janet Adkins, a 54-year-old woman with probable Alzheimer's disease whose suicide Dr Jack Kevorkian aided with the use of his suicide machine. There are no laws in Michigan prohibiting physician-assisted suicide, and therefore Dr Kevorkian was initially charged with murder. But those charges were later dropped. Dr Kevorkian also recently assisted in the suicides of two other women in Michigan.

Advance directives constitute one end of the spectrum of patient self-determination . . . the other end . . . is physician-assisted suicide.

Dr Timothy Quill of Rochester, New York advanced the debate in March, 1991, by revealing his participation in the suicide of his patient, Diane, a 46-year-old woman with acute leukemia who elected not to undergo chemotherapy – treatment which had a 25% likelihood of success, odds Diane thought were too low.[5] Dr Quill had extensive discussions with his patient; he had known her for eight years and had seen her battle alcoholism and poor self-esteem. She emerged as a strong, self-possessed artist whose decision to end her life was one that Dr Quill respected. Dr Quill presented, at her request, the barbiturates she subsequently used to end her life. He told her the dose for sleep, and the dose for suicide – She informed him of her plans, took the lethal dose quietly at home after saying good-bye to her family, and Dr Quill was notified two days later.

While both of these examples constitute physician-assisted suicide, they differ considerably from one another.

First, Dr Kevorkian did not have a long-standing relationship with the patient, was not involved in her current care, and was not specially trained in assessing depression. Also, Mrs Adkins was not terminally ill.

Does that make what he did any less ethical than what Dr Quill did? Did Dr Kevorkian perform euthanasia or assist a person in committing suicide? Unlike Dr Kevorkian, Dr Quill had a long-standing relationship with the patient, and was involved in her current care. Were his actions more morally justified as a result of this long-standing relationship?

Such comparisons deflect discussion from the main issue at hand.

Is it ethical for a physician to ever assist a patient who wishes to commit suicide? Are there gray zones? If a doctor injects the drug that leads to death, is this euthanasia or is it still an assisted suicide? Is the physician's act more reprehensible if the patient does not ask to die, but the physician feels it is in the patient's best interests to do so? Where are the moral, ethical limits? What is the line beyond which physicians should not cross in assisting patients with death?

Thousands of years of medical belief state that providing assistance in committing suicide is unethical. The Hippocratic Oath notes: I will give no deadly medicine to anyone if asked, nor suggest any such counsel . . . First, do no harm.

Should Physicians Assist Patients in Committing Suicide?

The American College of Physician's Ethics Manual has said no. "Although a patient may refuse a medical intervention and the physician may comply with this refusal, the physician must never intentionally and directly cause death or assist a patient to commit suicide."[6]

The American Medical Association has said no. "In assisted suicide . . . the primary purpose of treatment is to cause death. And that purpose has no role in the professional responsibilities of the physician."[6]

The State of Michigan through its Board of Medicine has said no – they voted 8 to 0 to suspend Dr Kevorkian's license for helping three women commit suicide. "I think it would behoove us to let the world know we do not consider this as an acceptable practice of medicine", said one board member in Michigan.

The State of Washington has said no by turning down a referendum brought to the voters on Election Day known as Initiative 119, 54 to 40%. This measure would have permitted "physician's aid in dying" defined as "a medical service provided in person by a physician that will end the life of a conscious and mentally competent qualified person in a dignified, painless and humane manner, when requested voluntarily by the patient through a written directive executed at the time the service is desired."

What is the line beyond which physicians should not cross in assisting patients with death?

Physician-assisted suicide or permission to allow physicians to provide aid in dying goes beyond what this society should allow as an acceptable medical standard of care. It should not be viewed as an option in lieu of treatment, nor should it be made readily available to both doctors and patients who could abuse this activity, as Dr Kevorkian has done.

Here are questions that need to be answered in order to advance the debate.

1) *Should physician's aid in dying become a standard part of terminal care?* No. The right to die does not mean the duty to die, and some patients and doctors might review such a standard of care as obligatory. A patient may feel obliged to ask for such an option, and a doctor may feel obligated to offer such an option if it becomes a standard of care.
2) *Are physicians capable of assessing the mental competence of the patient so as to rule out depression as a confounder in the patient's desire for suicide?* Not always. Depression, medication may cloud the patient's judgment and prevent him or her from making a rational decision about suicide. In a patient who wishes to engage a physician in his or her suicide, the doctor must distinguish between depression that develops as a response to serious illness, and a clinical depression that can improve with treatment. In the latter case, the patient may subsequently lose all interest in suicide.[7]
3) *Can or should physicians assist patients in dying who are not competent?* Why should Dr Quill not prescribe barbiturates to an incompetent patient dying of leukemia who will go through just as much pain and suffering as his patient, Diane who *was* competent.
4) *If society allows the practice of "physician's aid in dying," will "euthanasia clinics" or worse, "suicide mills" emerge where people will travel long distances to have someone assist them in dying, as was the case with Dr Kevorkian?*

An ignominious distinction for a state. Interestingly though, there seems to be a gray zone here; a place where the public and the medical profession view a doctor's actions as morally justified, but do not want to go so far as to legally sanction such action. For example, the American College of Physicians, despite its Ethics Committee statement against such behavior, wrote a letter to the Assistant District Attorney in Rochester commending Dr Quill for his courage in forcing the ACP to reevaluate the physicians' role in this issue. They stated their view that he acted "ethically and humanely and in the highest traditions of our profession." (They recommended that charges against Dr Quill be dropped.)

Conclusion

Every human being deserves to die with dignity. The medical profession must play an active role in helping patients achieve this goal. Outlining the patient's wishes for terminal care is one way of assisting patients in dying. However, assisting patients in committing suicide is not.

Maintaining the illegality of physician-assisted suicide provides a safeguard against abuse.

Maintaining the illegality of physician-assisted suicide provides a safeguard against abuse. Here is the gray zone, the irony, and perhaps the solution. A practice can be ethical under certain circumstances; it can be compassionate and humane, but illegal nonetheless. As expressed by Misbin

in a recent *New England Journal of Medicine* article, the obligation of the physician must be to keep such occasions as rare as possible by addressing the issue of advance directives and terminal care as aggressively as possible.[4] There is no role for government in regulating and overseeing physician's aid in dying as Initiative 119 sought to do. This activity must remain in the domain of the patient-physician relationship. This is a privileged, intimate relationship that should be shielded from government intervention. Should physician-assisted suicide be legally sanctioned? No. Can such action ever be considered ethical nonetheless? Yes.

What should society expect from this debate? The best response the medical profession can make to the physician-assisted suicide or euthanasia movement is to:

1) *Provide better terminal care.*
   Investing in programs like Hospice is an example. Terminal and palliative care needs to be expanded, strengthened, and seen as an option for everyone suffering from a terminal illness, or in the case of Alzheimer's disease, a horribly debilitating one.
   Improved terminal care also includes:
   • Access to terminal care providers, like Hospice, at earlier stages in a patient's disease.
   • Better pain management and control.
   • Holding back from recommendations of grandiose, expensive medical technological therapies that may be of limited benefit to patients.
2) The provider community including physicians and institutions should encourage healthy patients to take advantage of the advance directives that are available to them. Living Wills and Durable Power of Attorney for Health Care forms could yield enormous benefit to patients before the end stage of an illness.

Finally, members of the medical profession must work with their patients and help them accept dying as a part of life that brings family and loved ones together. If the patient is pain-free and at peace, the physician's role can be one of supporter and helper, assisting in the painless, humane letting go of life.

References

1. Arns GJ, Arnold B, Aroskar M, et al. Bioethicists' Statement on the US Supreme Court's Cruzan Decision. NEJM 1990; 323:686-7.
2. Greco PJ, Schulman KA, Lavizzo-Mourey R, Hansen-Flaschen J. The Patient Self-Determination Act and the Future of Advance Directives. Annals of Internal Medicine, 1991; 115:639-643.
3. Kjellstrand CM. Who Should Decide About Your Death? Editorial, JAMA 1992; 267:103-4.
4. Misbin RI,. Physicians' Aid in Dying. Sounding Board, NEJM 1991; 325:1307-11.
5. Quill TE. Death and Dignity – A Case of Individualized Decision Making. Sounding Board, NEJM 1991; 324:691-4.
6. Weiner J, Snyder L, Federman DD. Ms. Washington is Terminally Ill and Wants to Die–Should Dr Jones Assist? Case Study, ACP Observer, November 1991.
7. Conwell Y, Caine ED, Rational Suicide and the Right to Die–Reality and Myth. Sounding Board, NEJM 1991; 325:1100-2.

Address correspondence to:
Barbara A. DeBuono, MD, MPH
RI Department of Health
3 Capitol Hill
Providence, RI 02908

RHODE ISLAND

Excellent opportunities in urgent care facilities for career oriented physicians. Competitive salary and benefits.

(401) 943-4540

or send CV to:

Anthony Migliaccio, MD
Medical Director
Northeast Health Care, Inc.
495 Atwood Avenue
Cranston, RI 02920

The Hospice Response to Proposals of Assisted Suicide

David Rehm, ACSW
Edward Martin, MD

The public perceives a loss of control over end-of-life decisions, fearing technology run amuck and out of control, compromising a dying patient's dignity and autonomy.

Recently the voters of the state of Washington narrowly defeated Initiative 119 which would have legalized physician-assisted suicide. Similar proposals will be voted on in other states in coming months and years. That a perceived need for physician-assisted suicide is so widespread points to a terrible deficiency in the way our health care system is seen to manage terminal illness. The public perceives a loss of control over end-of-life decision, fearing technology run amuck and out of control, compromising a dying patient's dignity and autonomy. Physician-assisted suicide is seen by many as the only alternative to a high-tech, institutional death.

Final Exit, a book which gives detailed instructions on how to commit suicide is intended for terminally ill patients. The book rose to the top of the best seller list where it has remained. Many bookstores have had trouble keeping the book in stock. In her foreword to *Final Exit*, Betty Rollins states her mother had "nothing but nausea and this pain." In his introduction, Derek Humphrey, founder of the Hemlock Society, recalls that he sought to assist his wife in her suicide because he was "unable to bear to see her suffering." It is not surprising that given their experiences with uncontrolled symptoms and the suffering that ensued, that assisted suicide would seem to be the answer. But must we continue to accept poor symptom control as simply part of the dying process? All of us working in hospice have heard in response to request for pain medication the explanation "of course he has pain – he has cancer." This, however, is totally unacceptable; and allowing patients to die without vigorous attention to symptom control simply represents poor medical care.

Most of the measures which would legalize assisted suicide incorporate some requirement that the illness is, in fact terminal, with a prognosis of less than six months. This is, of course, problematic. At hospice where a similar life expectancy criteria is used for admission, we expect that some patients will outlive their original prognosis. In fact, some patients improve and are discharged from the program then readmitted months or years later after their disease again progresses. Patients who elect the suicide option would have no such second chance.

Our experience at Hospice Care of Rhode Island has clearly shown that suicidal ideation is an extremely commonplace occurrence amongst those who are terminally ill. Many patients choose to share these thoughts with our staff and volunteers which has afforded us an opportunity to explore with our patients, these thoughts and their related emotions. While a portion of these patients experience a true clinical depression, the majority respond to a variety of fears and concerns which can be addressed quite readily. For those patients on the hospice program, the fear of being sustained in a vegetative state against their wishes has been, for the most part, resolved by their election of the hospice palliative care program. Fear of a lingering death tormented by pain is, however, very common. As mentioned above this is particularly troubling to the hospice practitioner since modern palliative care renders such fears virtually unfounded.

Another pervasive source of patient anxiety is loss of control as their illness progresses. While the physical

David Rehm, ACSW, is the Executive Director of Hospice Care of Rhode Island.

Edward Martin, MD, is Medical Director, Hospice Care of Rhode Island, and Clinical Instructor of Medicine, Brown University, Providence, Rhode Island.

progress of the disease may be unavoidable we can mitigate this fear by ensuring that the patient maintains control over the decisions affecting his/her care.

. . . must we continue to accept poor symptom control as simply part of the dying process?

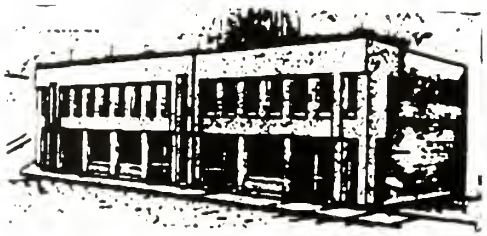
A fourth source of frequent patient concern is that they will become an intolerable burden to their family. Here again it is possible to identify and address these concerns openly in the majority of cases through the intensive support now provided by the Hospice Care of Rhode Island team of professionals and volunteers.

The result of this approach over the last thirteen years is quite clear. When the patient is offered physician-supervised palliative care, is put in control of his or her own treatment decision-making, and adequate support is provided to the family caregivers, the suicide option is no longer necessary. In fact, Hospice Care of Rhode Island has now served well over three thousand patients and to our knowledge only two of those deaths have come as a result of suicide. This experience leaves us with the conviction that for a great many of those Americans looking to suicide as a means to deal with the end of life, hospice provides a very real and effective alternative.

It should come as no surprise, therefore, that many members of the hospice movement led the effort to defeat Initiative 119 in Washington. With that effort comes the responsibility to make medical practitioners, as well as citizens, aware of the hospice alternatives. An even broader social challenge comes in the responsibility to provide adequate access to high quality terminal care. Unfortunately in our current economic climate this is a goal that may be out of reach for the 35 million Americans who have no medical coverage. For this group of citizens *Final Exit* looms as possibly the only alternative to a death bereft of dignity.

For those with terminal disease who choose not to enter a hospice program there remains a need for good palliative care and attention to symptom control even if aggressive treatments are to be continued. There is no reason not to insist on attention to pain control for all patients. Health professionals from around Rhode Island have now come together to form the Rhode Island Pain Initiative. This group will begin to identify barriers to good pain control and propose solutions. It will take a concerted effort to make comprehensive pain management a basic part of acceptable health care to be expected and insisted on both by patients and medical practitioners.

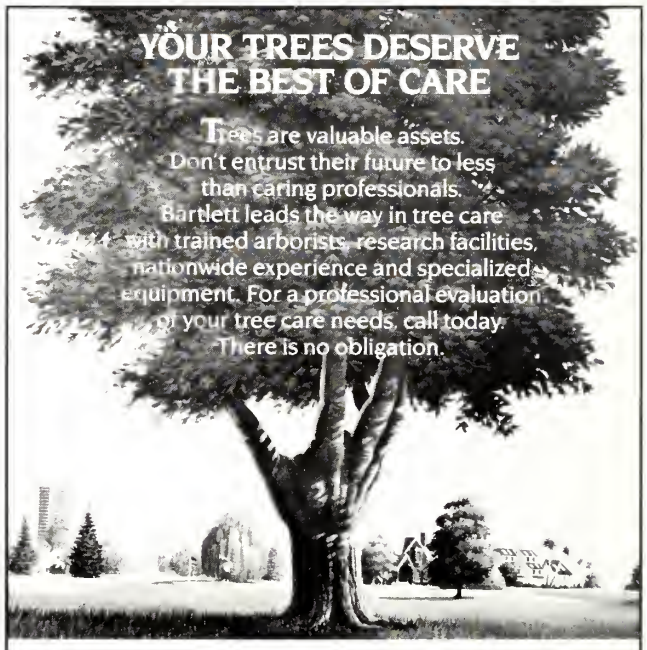
CONDOMINIUMS
FOR SALE OR LEASE



845 NORTH MAIN STREET
PROVIDENCE, RI

• Professional Office and Retail Space
• Convenient Access to I-95
• Minutes from downtown Providence, the Hospitals and Universities
• Ample On-Site Parking

CONTACT: CINDY MORSE, CCIM
PETER M. SCOTTI & ASSOCIATES
60 Ship Street, Providence, RI 02903
CCIM
401-421-8888


YOUR TREES DESERVE THE BEST OF CARE
Trees are valuable assets. Don't entrust their future to less than caring professionals. Bartlett leads the way in tree care with trained arborists, research facilities, nationwide experience and specialized equipment. For a professional evaluation of your tree care needs, call today. There is no obligation.

All Phases of Tree Care: Residential and Commercial

LOCAL OFFICES:
Seekonk, MA
508-336-9330
North Kingston, RI
401-884-2885

BARTLETT
Scientific tree care since 1907
BARTLETT TREE EXPERTS
Corporate Office: STAMFORD, CT

Backed by the Bartlett Research Laboratories and Experimental Grounds
Charlotte, North Carolina
©1991 Bartlett Tree Experts

Physician-Assisted Suicide: A Battle of Technology and Morality

David A. Ames, D. Min.

It is the duty and practice of physicians always to assist their patients in the wonderful and awesome task of both living and dying well.

The only thing approaching an absolute in the practice of medicine is the two-fold principle of doing good and of not doing harm. I disagree with those who err on the side of making technology an absolute. They would hold that, once a patient is attached to a life-support system, it is wrong to disconnect the system even when it is clear the patient will not recover and will die. I also disagree with those who err on the side of making patient autonomy an absolute. They would hold that the patient's desires are decisive; if the patient produces "clear and convincing evidence" they have no desire to continue treatment, then the physician is obligated to discontinue or withhold treatment even if the therapy shows definite promise of a good outcome. The first position, that of making technology an absolute, makes us humans slaves of the very devices we have crafted to serve us. The second position, that of making autonomy an absolute, makes us completely self-sufficient and independent beings free of any relational responsibility or accountability. Both of these positions are reactions to the medicalization and the secularization of society and culture.

David A. Ames, D. Min., is Episcopal Chaplain for Brown University and Rhode Island School of Design, Providence, Rhode Island.

I am not suggesting that physician-assisted suicide is always wrong. Nor am I suggesting it should be accepted practice. It is the duty and practice of physicians always to assist their patient in the wonderful and awesome task of both living and dying well. To these ends, living well and dying well, the physician may be called upon to practice preventive medicine, to prescribe drugs for pain and symptomatic relief, and to participate in decisions either to do something or not to do something which will result in their patient's death. What is more significant now than ever before, is that physicians have the education, training, and experience necessary to make good judgments in understanding and caring with and for others.

When is physician-assisted suicide considered to be a good judgment? When is physician-assisted suicide not to be tolerated? By asking these questions in this way I am suggesting that there are times when physician-assisted suicide may be considered a relative good and there are times when it is clearly wrong or evil.

Joseph Fletcher, a pioneer in the field of medical ethics and one of my ethics professors, died this past October. He was 86 years old and suffered from cardiovascular disease. He began the modern debate in medical ethics with the publication in 1954 of *Morals and Medicine*. He continued provoking critical thought in his book, *Situation Ethics*, published in 1966 and in *Humanhood: Essays in Biomedical Ethics* in 1979. He argued the case for active euthanasia, for suicide as "the signature of freedom," and for love as the only intrinsic good. In many ways he was on the leading edge of ethical debate in theology, medicine, law, and business. He defined euthanasia simply as "merciful release from incurable suffering" and acknowledged how the physician's promises to relieve suffering and to prolong and protect life are sometimes incompatible and present "a troubling problem of conscience in medical care." Fletcher concluded that "personality is supreme over mere life. To prolong life uselessly, while the personal qualities of freedom, knowledge, self-possession and control, and responsibility are sacrificed is to attack the moral status of a person."[1] In 1983, after recovering from cardiovascular surgery, Dr

Fletcher told me, "I learned something about myself in relation to all that I have been writing and speaking about with respect to euthanasia over the years. It's all true."[2] The teacher of personal experience is the best verification of knowledge; and in my experience Joe Fletcher was one who always spoke critically both from the heart and the mind and with kindness and compassion for others.

A case now in the court in Quebec has stirred debate on the question of physician-assisted suicide. A 24-year-old woman identified as Nancy B suffers with a neurological disease known as Guillain-Barrè syndrome. The disease has advanced to such an extent that she has irreversible neurological damage and is paralyzed and unable to breathe without a respirator. Federal law in Canada, as in the US, prohibits euthanasia, suicide and assisting suicide. Nancy B is articulate and has said, "I am fed up with living on a respirator; this is no longer a life . . . I do not want to live. The only thing I have is television and looking at the walls. It's enough. It's been 2-1/2 years that I've been on this thing and I think I've done my best."[3]

Is withdrawing respirator support . . . equivalent to physician-assisted suicide?

Several questions come to mind with respect to Nancy B. Whose decision is it? Is withdrawing respirator support in her case equivalent to physician-assisted suicide? Does Nancy B have a right to refuse further respirator support? If the court concurs with her request, who should turn off the respirator?

Recently, I presented this situation to a class of chaplain interns. They all agreed the decision was properly the patient's and her family's, and that she does have the right to refuse further respirator support. They weren't so clear that the physician should be the person to turn off the respirator, and they were even less clear when I suggested if not the physician then why not the chaplain?

The concern here focuses on our understanding of life and what constitutes a life worth living. I don't know Nancy B, but I would want the decision to turn off the respirator to be carried out in the most humane and caring manner. Once the patient, family, physicians and others related to Nancy B agree that "this is no longer a life," her death becomes a sacred moment in recognizing life's end. Jewish and Christian traditions provide for pastoral and sacramental ministries at the end of life. Opportunity for reconciliation, for forgiveness and absolution, for saying good-by, for invoking God's blessing on the patient and everyone present should be provided. And, in Nancy B's case, the person she trusts and designates, providing that person is willing to accept the ritual task without fear or guilt, should be the one who turns off the respirator. There are many physicians who would do this merciful, kind, and compassionate act for their patients. There are also chaplains who would do the same.

The case of Nancy B is similar to one reported a year ago in the *New England Journal of Medicine* by Dr Timothy Quill. It concerned a patient of his, Diane, who following a bone marrow biopsy was confirmed as having acute myelomonocytic leukemia. Without treatment, this type of leukemia results in certain death in days, weeks or at most a few months. With treatment, involving induction chemotherapy followed by consolidation chemotherapy, and if still alive, bone marrow transplantations, survival is about 25%. Diane, after conversations with her doctor, husband and son, refused to undergo chemotherapy and wanted to spend whatever time she had left outside the hospital. Dr Quill continued to meet with her on several occasions and was troubled by her giving up on a 25% chance of long-term survival. They had a second hematology consultation and talked about the meaning and implications of treatment and nontreatment. Diane consulted with a psychologist; they arranged for hospice care, and they left open the possibility that she would change her mind.

Over a period of several months Diane had two serious infections that responded well to empirical courses of oral antibiotics. There were three tumultuous months, followed by two weeks of relative calm and well-being. Then, bone pain, weakness, fatigue and fevers dominated her life. Earlier, Diane had requested barbiturates for sleep. Dr Quill became certain that she knew how to use them for sleep, and also that she knew the amount needed to commit suicide. When it became clear that the end was approaching she said her final good-byes to her husband and son one morning, and asked to be alone for an hour. After an hour, she was found dead on the couch and seemed to be at peace.

Dr Quill was called, and in turn, called the medical examiner to inform him that a hospice patient had died of "acute leukemia." No mention was made of suicide.

Timothy Quill had some questions about social constraints around decisions about dying. He asked how many families and physicians secretly help patients over the edge into death who are suffering severely; how many patients take their own lives, often alone in despair; whether the image of Diane's dying alone will persist in the minds of her family; and whether her method of death was the most benign.[4]

Richard McCormick, SJ, Professor of Christian Ethics at the University of Notre Dame, sees the issue of physician-assisted suicide as the "culmination of at least five cultural trends." These are: the absolutization of autonomy; the secularization of medicine; the inadequate management of pain; the nutrition-hydration debate; and the financial pressure of health care.[5] It is Fr McCormick's view that the debate about physician-assisted suicide is a reaction to these cultural trends and represents our failure as a society to respond to them.

In contrast to McCormick's view, the American Medical Association understands the issue as a result of new technologies. An editorial in the

Journal of the American Medical Association suggests "we should recognize three points: (1) This problem (the termination of life support) is entirely new. It has been brought to the surface by technology that is new. (2) These questions are both individual and societal. They are societal in that the community sets the limits within which patient autonomy can operate. Society must also consider the costs of individual decisions to society as a whole. In this sense, these problems must be addressed by societal agencies (legislatures and courts) counseled by the expert knowledge of physicians, philosophers, and theologians. Paradoxically, the power of scientific medicine has created a problem so fundamental that it has moved beyond the boundaries of medicine. (3) Any satisfactory solution will defend the dignity and integrity of individual humans."[6]

The problem is, in my view, not one that is "beyond the boundaries of medicine." It is true that new technologies have brought troubling issues and problems to the surface. But, it is also true that the "secularization of medicine" and the "absolutization of autonomy" cause the kind of reaction and demand for assisted death we are now witnessing. Our society has lost a sense of moral direction and has substituted economic value and worth for human compassion. The over-emphasis on patient autonomy has devalued the importance of the community and relationships which reflect mutual trust and respect and the essential interdependence which makes up the fabric of a just social order. It is my conviction that religion has a critical role and function in this context. It has a history and is a living tradition of the meaning of covenant relationship through which trust, compassion, kindness and mercy are both possible and realized.

Mark Duntley, Jr, Chaplain and Assistant Professor of Religious Studies at Lewis and Clark College, addresses this concern when he writes, "At the heart of caring is the concept of mercy. Mercy or compassion toward the dying and suffering seems to be central to any philosophy of healing, and most certainly is the primary argument of the morality of euthanasia. If prolonging painful or insentient existence can be cured, then the responsibility to care for another human being may indeed require ending his or her struggle. The key issue is determining the circumstances in which physician-assisted suicide is indeed merciful treatment. Understanding mercy will help determine those circumstances."[7]

Duntley proceeds to argue for mercy as understood in the context of covenantal relationships. He sees this as going beyond the customary and legal boundaries of contractual relationships which define most of physician-patient interactions.[8] "Without an appropriate covenantal context for mercy, assisted suicide lacks moral force and sanction. Unfortunately, neither our health-care system nor our general attitude toward health-care providers encourages us to seek covenantal relationships with our physicians. On the one hand, the system tends to encourage technical specialization and cost management over physician-patient relationships. On the other hand, we tend to think of physicians as omniscient miracle workers who should always be able to cure us."[9] The task, Duntley concludes, is to transform "our contractual system of 'consumer ethics' into one based on personal relationships, mutual interest, the common good and 'covenantal ethics'."[10]

Death happens to each one of us as human beings. Death is also something we do; we do it to ourselves and we do it to others. One major problem is to recognize the reality and to accept it. I admit that in itself is difficult in a culture that thrives on denying the reality of death and in a profession (medicine) that is dedicated to the preservation of life and the curing of diseases. Nevertheless, death is real, it happens, and there is no escape from it. What matters is how and when death happens to us as individuals. We yearn for long lives, free of physical pain and suffering, healthy and functioning well throughout the years. The matter of participating in the *how* or the manner of one's death is an essential part of acting in freedom. For hundreds of years Christians have prayed about death in "The Great Litany". They ask God's deliverance "from all oppression, conspiracy and rebelling; from violence, battle, murder; and from dying suddenly and unprepared."[11] Death is itself an act of faith, faith in the resurrection, in new life, in victory over death. Life has meaning and purpose, and the natural event of death which in God's time, comes to all mortal persons, is the beginning of the completion of life. Christian ethics as well as Christian prayer requires people of faith to participate in their own dying.

This historic prohibition of suicide must now be jettisoned as outdated and irrelevant to our contemporary practices of medicine and religion.

Early Christians followed the Jewish tradition in opposing suicide. Physiological life was considered "sacrosanct and untouchable." "St. Augustine cast aside the observation that the Scripture nowhere condemned suicide, and that they even reported without comment or condemnation the suicides of Ahithophel by hanging, Zimri by fire, Abimelech by sword, Samson by crushing, and Saul by sword. He said with fine simplicity that the Scriptures nowhere *authorizes* us to eliminate ourselves. This became the conventional Christian position, and St Thomas Aquinas gave it its classical form in the saying, 'Suicide is the most fatal of sins, because it cannot be repented of'."[12] This historic prohibition of suicide must now be jettisoned as outdated and irrelevant to our contemporary practices of medicine and religion.

Charles Meyer, Assistant Vice President of Patient Services at St David's Hospital in Austin, Texas has written, "The church's historic condemnation of assisted death is based on outdated knowledge, unaware of the extremes created by biomedical technology. The traditional sanctity of

life arguments no longer apply when we are faced with new situations – such as persistent vegetative states, comas, and numerous congenital or drug-induced anomalies – that *look* like 'life' but are not. We must come to terms with the fact that some of the 'life' we have created or into which we have ventured is *not* sacred, or in need of protection and preservation at all costs.

"In fact, the opposite is true. To truly preserve what it has traditionally held to be the 'sanctity of life', the church must become a willing partner in the development of carefully circumscribed guidelines permitting the passive and active hastening of death. To do less than that is to capitulate responsibility to medical technology and to condemn people to horrid deaths to which we would not submit our animals."[13]

The traditional sanctity of life arguments no longer apply when we are faced with new situations – such as persistent vegetative states, comas, and numerous congenital or drug-induced anomalies – that look like 'life' but are not.

Statutes have been enacted over the last ten to twenty years concerning the definition and determination of death, durable powers of attorney for health care, and living wills. The Patient Self-Determination Act, now in effect, mandates that patients entering health care institutions must be given the option to express their desires in writing. There is a wide range of response to all this; there is also a wide range of education and sophistication about using these documents. Some people will say they're not interested in exercising their legal option. Some will merely sign on the bottom line and name a next of kin or a friend without much consideration. And others will want to be very explicit covering every conceivable event they can imagine as well as consulting with their physician, lawyer, clergyperson, and designated agent. There is also a wide range of training offered to professional groups and health care administrators about these documents. Even with these documents it is an open question whether many physicians would, as in the case of Nancy B, actually assist in a patient's desire to turn off the respirator or to withdraw treatment even when medical prognosis is no longer positive.

There are several steps I would recommend in responding to the concerns raised in this article about physician-assisted suicide: The first concerns hospital chaplains and clergy of all denominations. They should make the issue of death and physician-assisted deaths, including suicide, a priority for their own continuing education. Second, courses in death and dying should be required as part of medical school education. Such courses should include suicide and euthanasia, religious rituals for the sick and dying, pain control, the psycho-social needs of terminally ill patients, legal issues, and advance directives. Third, institutional ethics committees should develop policies and guidelines about their use of advance directives and decisions affecting terminal illness and patient death. Within the context of each of these recommendations consideration should be given to our common understandings of the meaning of human life and the significance of death. For example, medical students might be asked to participate in an exercise of filling out their own death certificates and discussing what they put down and how they arrived at a particular time, circumstance and cause. Chaplains and clergy might witness an autopsy and discuss their feelings about respect for life and the issues encountered in administering to dying patients and their families. Institutional ethics committees, with other interested parties, might come together for an interdisciplinary seminar on the subject of death and physician-assisted death.

The real task is for us all to address the religious, moral, and public value questions and issues related to physician-assisted suicide so that our ethical behavior can be responsive to and in control of our technological prowess. Death is too important, too human to be given over to the control of either machines, drugs or the courts. Death is too much a part of life; we therefore need to foster both the freedom to decide how to live and what we wish to contribute to others with our lives, and we need the freedom to decide how to die and what sort of life will be "no longer a life" either for us or for those with whom we have been in relationship.

References

1. Fletcher, Joseph. Morals and Medicine, 1594, p. 191.
2. This comment was made in a personal conversation we had in Cambridge, Massachusetts.
3. *The New York Times*, December 1, 1991.
4. Quill Timothy E. MD. "A Case of Individualized Decision Making," *New England Journal of Medicine*, 324:10; March 7, 1991. (These two cases are remarkably different from those of Dr Jack Kevorkian. I commented on the case of Janet Adkins in "Ethical Issues at the End of Life," *Rhode Island Medical Journal* 73:8, 1990, 367-372.
5. The Christian Century, December 4, 1991, 1132-1134.
6. *JAMA*, April 25 1990, 263:16, 2221.
7. Duntley Mark A, Jr. "Covenantal Ethics and Care for the Dying, The Christian Century, December 4, 1991, 1135-1137.
8. He refers to the work of William F. May, The Physicians Covenant, Westminster Press, 1983.
9. Duntley Mark A, Jr. op cit, p. 136.
10. Ibid, p. 1137
11. The Book of Common Prayer, 1979, p. 149.
12. Fletcher Joseph. Morals and Medicine, op cit, p. 178-9.
13. Meyer Charles. "Hastening the Inevitable," excerpted from the book *Surviving Death* and published in *The Witness*, February, 1991.

The Ethics of Research in Incurable Disease

Lester S. Adelman, MD

Such principles as good science, truth-telling and informed consent are much the same whether the patient's disease is serious or trivial, curable or fatal.

Clinical research in incurable disease in most aspects is no different from any clinical research. In fact, since research in *curable* disease is often an adjustment in treatment, research in *incurable* disease is the paradigm for ethical considerations in all clinical research. Such principles as good science, truth-telling and informed consent are much the same whether the patient's disease is serious or trivial, curable or fatal. Nevertheless there are several aspects of research using patients with incurable disease which are sufficiently different as to merit separate consideration. The circumstances of these patients makes it especially important for researchers to be sure that the ethical aspects of their experiments are clearly thought out. There are important societal pressures on patients and researchers alike that must be considered in the design of clinical trials in this group of patients.

By incurable disease I mean a disease for which there is no effective treatment, and which is likely to be fatal within a short period of time (perhaps 2-3 years). I have in mind such diseases as rapidly fatal carcinoma, amyotrophic lateral sclerosis and glioblastoma multiforme. Incurable diseases such as multiple sclerosis, which are usually associated with a more prolonged clinical course present a different set of problems.

Lester S. Adelman, MD, is Professor of Pathology (Neuropathology) and Associate Professor of Neurology at Tufts University School of Medicine, Boston, MA.

Truth-Telling

American medicine has undergone a revolution in attitude about truth-telling during the last 30 years. It was still common when I was a medical student in the early 1960s to withhold the truth from patients with incurable disease. Now, in the 1990s, an American physician who does not tell a patient his diagnosis and prognosis is expected to be able to justify this action by citing some special circumstances which argue against such disclosure. I have stressed the American nature of this revolution because in many parts of Europe and Japan it is still considered cruel to burden the incurable with the details of their prognosis. This change in American values comes mainly from our respect for patient's rights, particularly the right of autonomy. For a patient to exercise the right of autonomy in decision making he needs to have the facts on which to base his decisions. This is particularly true if the decisions have to do with participating in clinical trials and especially if he is suffering from an incurable disease. It has been argued that we Americans have come too far in our quest for truth-telling and autonomy, and that there is some validity in paternalistic attitude of doctors in other societies. Even if this were true it seems to me to be essential that patients we hope to involve in clinical trials know what their disease and prognosis is for them to be able to give informed consent for their participation in these experiments.

Informed Consent

The problem of informed consent has been discussed both from ethical and legal points of view. Doctors have despaired of getting a consent that is informed enough to satisfy the courts. Many patients and their families are incapable of understanding the facts and reasoning involved in complicated treatment decisions. After a recital of risks and benefits the physician is asked what he would do if he were the patient, and he then makes the decision for the patient or the family. These difficulties are real and common, but they are almost never germane to the decision to give consent to participate

in clinical trials in incurable disease.

The discovery of a drug like penicillin, which dramatically alters the course of disease, is a rare event, and the clinical trials required of such a drug are simple. Most treatments proposed for patients with incurable disease are unlikely to alter the course of the disease in the patient in the trial. Since the patient is unlikely to derive significant benefit from the trial it is impossible to help him make the decision to participate on paternalistic grounds. Researchers always feel optimistic about the potential of treatments which they are investigating, but the history of medicine teaches us that the overwhelming majority of treatments which we investigate are of no use. Thus the assumption is almost always that the treatment is unlikely to offer benefit to the patient.

Why then do doctors carry out clinical trials in incurable disease? The answer must be that through these trials the doctors hope to gain clues to further modification in treatment which may eventually be of aid to other patients with the same disease in the future.

Why do patients participate in the trials? The logical explanation is that they do so from motives of altruism. Recognizing that they are unlikely to benefit, they consent in order to help gain this knowledge which will benefit mankind, and in particular, patients suffering from the same disease which they have. The paradox is that patients with incurable disease may find it difficult, if not impossible, to believe that they will not benefit themselves. Since the prognosis is hopeless, they are willing to take any chance, however slim, of being helped or cured. The dilemma for the physician is how to explain to these patients how slim the chances of benefit really are without deflating the little hope that they have of getting effective treatment. The acceptance of the inevitable is a stepwise process and for long periods of time patients and their families can be aided by knowing that work is going on to try to treat the disease which they have. Participation in such trials can be an important source of consolation for patients.

Much medical research in years past was done on prisoners. Prisoners were encouraged to participate in such experiments as a way of repaying society for the crimes they had committed against it. Furthermore there were often explicit or implicit benefits in their conditions in prison. Modern ethicists have held that prisoners are incapable of giving truly uncoerced consent to participate in the research, and therefore, research using prisoners is unethical. It can be argued that patients with incurable disease are similarly incapable of giving informed consent and should not be used as research subjects.

For a patient to exercise the right of autonomy in decision making he needs to have the facts on which to base his decision.

Several differences between prisoners and these patients are worth stressing. The first is that prisoners have no vested interest in the disease being studied; it seems understandable for patients suffering from an incurable disease to want to help others with the same disease. Secondly, prisoners can be replaced in experiments requiring volunteers by uncoerced normal subjects, or by paid volunteers, but patients with a disease cannot be replaced by anyone else. (This is at least true for efficacy studies; studies of safety can be done in others.)

Experimental Design

The participation of patients in experiments from which they are unlikely to benefit places several burdens on the investigator. The use of such subjects demands that the experiments be well-designed, so that the gains in knowledge are as widely accepted as possible. We tend to take for granted that our experimental designs are valid; this is the area of our expertise. Yet, the history of clinical trials is filled with experiments whose design is so flawed that their results are cast into serious doubt. The obligation to design experiments well is a general one, and it applies to animal experiments as well as those on patients. The tragic circumstances of patients with incurable disease and their courage and altruism in allowing themselves to serve as subjects in experiments increases our responsibility to design the experiments as well as we can. This is an ethical as well as a scientific responsibility.

The Incompetent Patient

The incompetent subjects present additional problems in all clinical trials. Since they cannot give consent, others are asked to give consent for them. If the patient stands a reasonable chance of benefit, the decision is relatively easy. If, as I have argued, there is little chance of benefit to the patient in research in incurable disease, there is an inherent contradiction in asking someone else to consent for the patient on altruistic grounds. Altruism is a self-sacrifice; one cannot be altruistic for another.

This argument would preclude any trials in these patients. It has been argued, for example, that children should never be research subjects. Similar arguments can be raised for any incompetent patient; the mentally retarded, the mentally ill, and the demented. Since this would preclude clinical research in many diseases, most ethicists have been willing to concede that research, with little risk to the patient, which is centered on the patient's disease may be permitted. The principle of substituted judgment is invoked and the consent is based on an estimate of what the patient would have wanted if he were able to decide. This approach is more easily applied to the demented patient, who may have expressed an opinion on the subject when he was competent. It is harder to apply to those who have never been competent such as children and the mentally retarded. There are also problems in determining what amount of risk can be classified as "little risk".

Societal Pressures

The practice of clinical research is

different today from what it was 50 years ago. In the first place it is more apt to be successful. Basic science has provided the appropriate clues for many advances. New problems have come along with the success. The effective lobbying of the medical research establishment greatly increased the funds available for medical research, but also greatly increased society's expectations of what this work could achieve. Science reporters for the major newspapers and magazines need to write stories to fill their pages. The number of important advances announced in the press continues to raise expectations, even though most of these important advances are forgotten within a year or two.

. . . the history of medicine teaches us that the overwhelming majority of treatments which we investigate are of no use.

Relman took Eisenhower's warning about the Military-Industrial Complex and applied it to the Medical-Industrial Complex. There is yet another complex to beware of, the combination of the clinical researcher and the society for (or against) a specific disease. Societies such as the Muscular Dystrophy Association, the ALS Society, the American Cancer Society and the like have a vested interest in funding clinical trials that is stronger than that of such groups as the NIH. Many of these societies are sponsored and run by the families of patients with the disease in question. They are heavily biased, just as the patients are biased, toward the practical treatment of the disease in question. Their clinical advisors are physicians working in the field. These same physicians apply to the societies for grants to fund their own clinical trials. As physicians have become less competitive for NIH basic research grants, the physician-investigator has increasingly become the physician conducting clinical trials, often funded by the disease-oriented societies.

Of course the cooperation is mainly for the good. People with a personal interest in a particular disease help raise money for research on it, and seek the help of scientists actively engaged in the study of the disease to help them decide how to spend the money. That these same physicians are often the recipients of the grants is entirely understandable, and all of the societies are sensitive to the issues of favoritism that this situation raises.

My concern is that there is a hidden bias for the carrying out of clinical trials even though the basic science information that justifies the trial is not as strong as it might be. In such a situation the patients, the families, the societies, the researchers and the expert reviewers are all biased toward the trials, and there seems little opportunity to hear another voice.

Conclusions

Research in incurable disease is essential if cures or treatments are to be found. Although the ethical considerations are the same as for any clinical research, the desperate plight of these patients makes them vulnerable to exploitation. Physicians should be especially concerned that the consent of such patients to enter clinical trials is based on the patient's clear understanding of the nature of his disease, and particularly on his clear understanding of his motives for participating in the experiment. We need to be sensitive to the unconscious pressures on us to conduct clinical trials, and to be certain that the scientific basis and design of the experiments are as good as we can make them.

Address correspondence to:
Lester S. Adelman, MD
Tufts University School of Medicine
171 Harrison Avenue
Boston, MA 02111

For Diabetics: those with High Blood Pressure or Heart Disease

SCOT-TUSSIN® DM
cough & cold formula

Sugar-Free
No: Alcohol, Sorbitol, Saccharin, decongestant or sodium.

and

SCOT-TUSSIN®
DM Cough Chasers™
Sugar-Free Lozenges

1 (800) 638-SCOT or (401) 942-8555
SCOT-TUSSIN PHARMACAL CO., INC.
Cranston, R.I. 02920-0217

Ethical Dilemmas in America's Health Care System

Aging 2000 Staff
Charles Baldwin
Edward Caron
Christine Heenan
Adelaide Luber
Ira C. Magaziner
Lynn Margherio
Rita Michaelson
Rev William F. Nisi
Joan Retsinas
Renée Rose Shield
Marjorie Tarmey
Chip Young

Driven by the obligation to do no harm, physicians act only when they believe action might be effective.

America's health care system is today in a state of ethical turmoil. Fundamental questions about the values which should guide care are being widely debated in academia, government, religious organizations and in the health care professions.

Aging 2000, through its interviews has identified four issues which are being debated often in Rhode Island.

- Does our health care system provide sufficient equality of access to all citizens?
- Is our health care system too confrontational, relying too much on litigation and legal protection of the rights of patient and caregiver versus the building of trusting relationships?
- What are the obligations of family and society to care for dependent elderly people?
- Who should make decisions about the resources which are called forth to treat elderly patients, particularly near the end of their lives? Are there economic justifications for limiting the rights of individuals to receive the best possible care to preserve life or improve quality of life? Is it ever justifiable to terminate a life either actively or passively, by withholding nourishment or oxygen for example?

Today, decisions on these questions are often made on an ad hoc basis. Our health care system does not provide for ongoing, comprehensive ethical discussion. Unspoken assumptions often underlie the actions of participants.

The Decision-makers

There are a number of people and institutions who make decisions about health care. Each has a slightly different perspective on these ethical dilemmas.

The Physician

By virtue of expertise and professional authority, the physician exercises significant responsibility in making decisions about medical treatment. In doing so, the physician is guided by core values codified to some degree in professional canons of ethics.

The first value is one of life over death. A physician's primary responsibility is to preserve life. A second value is equality of access to care. A physician is supposed to treat all patients equally, battling to save lives regardless of the patient's race, age, gender, ethnicity, income, social class, character, personality or disability.

For the physician, these two values – life over death, and equal access – lead to a "propensity to treat." Regardless of the age, functional status of a patient or even in some cases, the patient's own wishes, the physician may feel a moral duty to treat the pneumonia, to order the feeding tube, to begin dialysis.

The physician, though, holds other values that can conflict with the "propensity to treat." The physician is obliged to do no harm, "*primum non nocere*." The physician may well wonder whether the short-term pain and discomfort of the spinal tap, the dialysis, and the surgery will bring long-term benefits. Treatment today involves a statistical weighing of odds.

Some medical journals suggest treatment for condition Y, while others are dubious. If the treatment fails, society might criticize the physician for "doing harm" and not allowing the patient to die. Yet, if a physician refuses to treat the patient, society might as easily criticize him or her for giving up too easily, for violating the medical duty to preserve life.

Driven by the obligation to do no harm, physicians act only when they believe action might be effective.

ABBREVIATIONS USED:

HCFA: Health Care Financing Administration

Hippocrates cautioned physicians to refuse to treat those who are overmastered by their diseases, realizing that in such cases medicine is powerless." Today's physicians, with their very large chest of technological tools, have more effective treatments to offer than their colleagues in Hippocrates' time. But many of today's physicians would concur with his statement.

Non-professional values also govern the physician's decision. The physician brings to medicine not just professional canons but also his or her own personal values, moral and religious convictions. Physicians are not required to perform treatment that violates those beliefs.

The physician brings to medicine not just professional canons but also his or her personal values as well as moral and religious convictions.

The nature of the physician-patient relationship is also changing. Older primary-care physicians were trained to see themselves in a parental relationship to patients. They offered advice and guidance, not primarily information. When the patient asked, "What should I do?" the physician responded authoritatively. In that exchange, the patient trusted the physician to offer advice in his best interest. That model worked best when the physician knew the patient well.

The physician might even decide not to tell a patient that the cancer was terminal, preferring to spare the patient the emotional pain of dealing with the "bad news". Medical journal articles of 30 years ago often debated the advisability of telling patients about terminal conditions and prospects.

While some physicians still operate this way, the "parental" role is no longer the norm. Specialization within medicine has produced increasing numbers of physicians who know more about individual parts of a patients's body than about the patient's life. And medicine itself now offers varied treatments for the same condition, including a choice among drug regimes. Physicians often don't want to answer the question, "What should I do?" Nor do patients want them to make the definitive decision alone. As the physician sees himself increasingly as a repository of expertise, so too the patient sees himself increasingly as a consumer.

This consumer and provider relationship creates a different type of physician role, the physician as engineer commenting on the feasibility of repairs to the arteries; the physician as contractor, willing to provide health care for a certain fee, for a specified period of time; and the physician as participant in a contract in which the patient and physician mutually decide what each expects of the other.

For chronically-ill patients, the contract model has become the norm. The physician cannot cure the chronic condition, but she or he can support the patient, managing pain and discomfort.

In the consumer/provider model, both the physician and the patient retain the right to terminate the agreement. While physicians may know their patients well, the model does not obligate the intimacy and commitment endemic to the "parental" model.

This new relationship, based on implied contract rather than trust contributes to the increase in malpractice litigation and "defensive medicine." There is a whole new ethical and legal debate about the rights of physicians versus the rights of patients in the implied contract. The confusion caused by this debate has frustrated many physicians and patients.

The Hospital

Hospitals have a stated mission to care for the sick, the ill and the dying. Many hospitals have created ethics committees to help guide their institution in carrying out this mission. Most of the time those values coincide with the physician's mission and the patient's wishes. Occasionally, however, they clash.

Clashes can end in court. If a physician orders the hospital to remove a feeding tube in a comatose patient and the hospital believes that such an action would violate its core values, then the courts find themselves at the center of the impasse.

Hospital nurses, guided by their own ethical canons, take as their mission, the alleviation of suffering and the care of the ill. This can bring them into conflict with physicians or the hospital.

In one case of a child born with Down's syndrome, parents refused to authorize a life-saving surgical procedure. Unsure of its chances for success and uncertain of the quality of life it could promise the surviving child, the hospital chose not to seek a court order to permit surgery. Without surgery, the child slowly starved to death. Although physicians tried to assure the nursing staff that the child was not in pain, nurses reported intense anguish as they passed the crib daily for five days.

In another example of conflict, Rhode Island's Marcia Gray case, the family was free to take the comatose patient home and withdraw treatment; yet when the family wanted the hospital to withdraw nourishment, the hospital director refused and the case ended up in court.

Hospitals share the physician's value of equality of access; they strive to treat all persons, regardless of race, ethnicity, social class or income. That basic value is underscored by federal law. The Hill-Burton Act requires hospitals that receive federal funds to serve a portion of uninsured patients who cannot pay for their care. Hospitals must, by law, treat even illegal aliens who have no Medicare cards and no legal status in this country.

For-profit hospitals are not supposed to "dump" non-paying patients onto public hospitals when those patients seek emergency care. Hospitals regularly factor unpaid debts and uncompensated care into their cost reports for the Health Care Financing Administration. Hospitals that serve a disproportionate number of poor people receive extra funds.

In the 1980s, hospitals implicitly

embraced a new value: economic survival. A hospital cannot fulfill its mission of serving people if it fails financially. Tighter Medicare reimbursement rules have forced hospitals to scrutinize carefully their patient populations, controlling lengths of stay and the services they provide. Communities need trauma centers, but a hospital may not be able to support one financially. A decision to close a center may be both harmful to the public's health and yet necessary for the hospital's economic survival. Conversely, hospitals may find that some services are more profitable. A hospital that specializes in those services may not be meeting critical health needs of the community, yet might justify specialization on the grounds of financial solvency.

Occasionally a hospital may find itself juggling obligations to the patient, to the physician and to its own financial stability. If a physician orders treatment X and the hospital does not grant that physician permission to perform that treatment within the hospital, or deems it unwarranted, the hospital can refuse to allow it to go on. A physician may want a patient to remain in the hospital after surgery but the hospital's own care plan timetables (based on Medicare's Diagnostic Related Groups), may require that the patient leave earlier. A physician must then appeal through appropriate channels to reverse this ruling.

Nursing Homes

Just like hospitals, nursing homes translate physician orders into care regimes. Unlike hospitals, nursing homes also try to offer a home-like setting. Nursing home residents, as opposed to hospital patients, live in the institution. And while the home may be a recuperative way-station for some residents, it is a last place of residence for others.

Nursing homes pursue three goals: therapeutic treatment, personal care in providing the requisites of home, including meals, housekeeping, sociability and at least a minimum level of autonomy. These goals do not dovetail comfortably. Nurses intent on distributing medications within specified times can rarely linger to chat about a baseball game or visit with a patient's family.

Nursing homes often must make decisions which violate individual autonomy – restraining patients with straps or administering psychotropic drugs which impair a patient's mental alertness. Recent regulations limit a nursing home's flexibility to restrain patients, but they are ambiguous and decisions are complex.

Insurers

Insurers play a central role in medical decision making. They choose or reject the treatments for which they will pay. Within the next 10 years, as more and more Americans are covered under "managed care plans," the vocabulary of utilization review will become as familiar to patients and families as it is now to physicians and institutions.

For very wealthy people, medical decisions need not include insurers. In the American free market medical system, patients may theoretically purchase whatever services they desire. Because medical treatment is so costly, however, the vast majority of people depend upon public and private insurers to pay for their care.

Insurers can say no to paying for treatments and their "no" is based on their operating values. The values, though, are not necessarily the same as physicians' or hospitals' values.

The well-being of one patient must be considered in the context of the whole insured population. In a classic risk-based system, individuals pool their premium payments, assured that those dollars will be sufficient to meet the needs of the group. The insurer is concerned with its total insured population. In this system, insurers ask, what treatments should the insured population pay for? Under what conditions?

Insurers also reject very costly treatments that hold little promise of success, even when they are potentially life-saving. Some people balk at this rejection, because it goes against the value to preserve life. Insurers, for example, will generally not cover liver transplants. Insurers may be reluctant to pay for newer diagnostic testing such as Positron Emission Tomography. Insurers also may pay only for a certain number of treatments, such as three in vitro fertilization attempts. When insurers deny coverage of treatment, they are raising the banner of community, instead of individual well-being.

The banner is valid, they argue, because the well-being of the community is not the sum of individual well-beings. They argue that there are a set number of people, who spend a finite number of dollars on health care. Everybody contributes dollars assuming that their combined contribution will pay the total group's expenses. If the group "maximizes" the health care of all individuals in the group, the pot of money may be too small. Either the insurer will need to scale back services, or raise premiums. Higher premiums may force some people out of the group, leaving them without insurance.

Also, many insurance companies operate as for-profit businesses, with obligations to shareholders. The pool of money must be large enough to give owners a satisfactory rate of return on their investment. If not, the company fails. An insolvent company doesn't just risk disappointing shareholders. It also leaves enrollees without coverage.

Nor do insurers operate under the same principle of equal access as physicians. All patients do not have equal access to treatment. Insurers may deny a liver transplant to an alcoholic, demand a certain level of disability before authorizing a hip replacement, require patients to contribute to the cost of care, and in doing so, restrict access.

Since a public program, Medicare, covers virtually all of the elderly population, most elderly people have not felt the new, dominant role of insurer in decisions about health care. To date, the federal Health Care Financing Administration (HCFA) has based decisions about Medicare coverage on the appropriateness of care. HCFA demands that vision loss reach

specified levels before it will authorize a cataract operation, for example.

Only recently have federal policy makers suggested limiting medical care because of costs. HCFA has tentatively proposed cost as a criteria for evaluating treatment. Public insurers have also followed their private counterparts in raising the copayments required of individuals to discourage excessive utilization of services. In proposing limitations on care, public insurers are basing their actions on the premise of maximizing care of the whole population.

The Individual

The United States is a pluralistic democratic society, shaped largely by immigrants from other nations, who brought distinct cultural traditions to this country. We honor individual differences, desires and traditions. We do not readily dictate to people what they "should" do, whether it is wearing seat belts, consuming alcohol or accepting blood transfusions. When religious beliefs cause patients to reject medical treatment, the courts sometimes intervene, asserting society's respect for life but usually society acknowledges the patients' values as well.

Earlier in this century, US Supreme Court Justice Benjamin Cardozo affirmed that, "Every human being of adult years and sound mind has a right to determine what shall be done to his own body; and a surgeon who performs an operation without his patient's consent commits an assault, of which he is liable in damages."[1] That decision (Schloendorff vs Society of New York Hospital) put the patient firmly in the center of medical decision making.

Until recently, however, patients rarely exercised the authority. Under the "parental" model of physician authority, the patient generally accepted the physician's word as above challenge. Several factors have caused individuals to reject that paternalistic authority and insert themselves into decisions.

First, the model of patient and physician relationships has changed. The physician no longer purports to know the person, his family or his values. The patient perceives himself as consumer. The patient is now an active participant in decisions about health care.

As the physician sees himself increasingly as a repository of expertise, so too the patient sees himself increasingly as a consumer.

Second, technological advances have created enough images for everyone to know that sustaining life at all costs may translate into a long limbo or a painful process of dying.

Third, the costs of health care have made us all question what should be the proper boundaries of care. Millions of children in America receive minimal health care. Is it right for a society to spend more resources on the last years of life, while spending relatively little on the first years? We are reluctant to answer that question by government policy, but we want individuals to pause before they choose costly treatment. Hence, the patient as well as the patient's family, become decision-makers.

To formalize that involvement, state governments have passed advance directive laws that authorize durable powers of attorney for health care purposes and living will documents that give people the option of refusing or specifying treatments, enabling them to assume some control over decisions formerly left to physicians. The recent federal Patient Self-Determination Act requires hospitals and nursing homes that participate in Medicare to discuss options for prior directives about care. The Act is designed to spur consciousness-raising among patients.

Now that the individual is firmly established as a decision-maker, ethicists ponder the problem of the chronically impaired, confused or demented patient, who cannot clearly articulate his or her wishes and values. Prior directives, involved family and court-appointed guardians provide partial solutions. But ethical dilemmas persist. For example, the prior directive states the individual's stance at one point in time. Would the 83-year-old woman reject treatment that she had rejected when she was 75? Also, family members bring to the treatment decision their own values, their own feelings about the patient, their own stances toward life. Family members may disagree as much about treatment as they do about other decisions.

In the period of disability before death, many people seem literally "moribund," as the process of dying may take not an hour or a week, but years. In that period, life continues but is severely compromised. For some people, dementia is the litmus test: they do not value a life in which they are incapable of having relationships. Others see total physical dependence and loss of autonomy as the boundary. Still others see life itself, however compromised, as worthy of sustaining.

Even a fully lucid hospital patient, who is ill and in pain, may not be able to sort through the long list of treatment options, much less understand them. Yet, informed consent has become a principle of medical ethics. The patient should understand what the treatment is and what it entails. However, the frail, ill person, faced with a long explanation, may "sign on the dotted line" only to expedite the process.

The Court

When conflict occurs, a court may be called upon to resolve the impasse. Court decisions are not uniform: a decision will vary with the judge, the state, the evidence.

The one fundamental right the courts have declared, since 1914, is that of personal autonomy: guided by informed consent, the competent adult may refuse life-saving medical treatment. Individuals have the right to say no to medical interventions, even after interventions have begun and even when interventions are not extraordinary. Recently a ventilator-dependent woman suffering from amyotrophic lateral sclerosis (ALS) asked the court to permit the hospital to disconnect her ventilator. The court agreed. In 1990, a Michigan court pronounced an 86-

year-old man competent to reject tube feeding.[2] Most courts, faced with competent adults, concur with the patient's wish to reject treatment. Although in rejecting life-sustaining measures, patients may violate core societal values, we allow them that freedom.

Is it right for a society to spend more resources on the last years of life, while spending relatively little on the first years?

Personal autonomy will also prevail even when the physician questions the wisdom of the patient's desire for life-prolonging treatment. In the case of Helga Wanglie,[3] the physician wanted to discontinue life support. The family objected, citing their belief that Mrs. Wanglie would want to be sustained. The court ruled for the family.

Similarly, when physicians have overruled patients' decisions and instituted life-sustaining measures, patients can sue. Edward Winter, an 84-year-old Ohio resident, asked his physician to put "do not resuscitate" on his medical chart. When Mr. Winter developed heart fibrillations, a nurse revived him. He sued the hospital for "wrongful life".[4]

The patient's autonomy carries forward even when he changes his mind. For example, an amyotrophic lateral sclerosis patient won her battle in court to have her feeding tube removed but then changed her mind. Her wishes were respected in both cases.[5]

If the courts usually have recognized the principle of personal autonomy when faced with a competent adult, they struggle to fashion general principles to guide decisions when faced with incompetent patients. The Nancy Cruzan case illustrates the extent to which courts can resolve a specific impasse, yet leave the underlying principles unclear.

In 1983 physicians first inserted a feeding tube into Nancy Cruzan. In November 1987, her family wanted it disconnected. Without court authorization, the hospital refused. The family petitioned the court for authorization. Missouri law required "clear and convincing evidence" of the patient's desires. While Nancy Cruzan had not made a prior directive (allowed under Missouri law), her family and a friend, as well as her physician, testified that she had indicated to them that she would not want the existence she now had. The judge granted the Cruzans' petition.

The Missouri Attorney General appealed, however. He wanted a higher court to set a clear precedent. The higher state court overturned the lower court. The US Supreme Court ruled, five to four, that Missouri could demand "clear and convincing evidence" of intent, and that Missouri could legitimately determine that the evidence of the witnesses did not meet that standard.

People looking for clear ethical principles – ones that will resolve the impasses – will not find them easily. While Missouri requires "clear and convincing evidence," other states do not. Some allow proxy decision makers, "substituted judgments," or less compelling evidence than the Cruzans presented.

The Unresolved Dilemmas

Underlying the dilemmas faced by all decision makers, is a health care system which has grown up with certain implicit ethics. Those who would fashion a health care system based on clear ethical principles must first understand the *de facto* ethics which pervade today's practice.

Inequality of Access

We have created a system where equality of access to health care does not exist. Many are uninsured. As insurance premiums increase and insurers offer multiple levels of coverage, wealth increasingly governs levels of access to health care. As insurance companies look increasingly toward financial performance, many try to "experience rate" their enrollees, meaning that insurance can be harder to get if you are ill.

As Medicaid and Medicare programs look to control costs, the gap between payments to doctors and nursing homes under these programs and private pay rates increase, causing some doctors and homes to refuse to take publicly financed patients.

Litigation Versus Trust

As doctor-patient relationships have become more distant and health care institutions more businesslike, and as the parental model of care has given way to a consumer-provider model, disputes have increased among doctors, institutions and patients. In our litigious society, these disputes often wind up in court. The fear of litigation affects the decisions of doctors and institutions. Defensive medicine, where practice is guided by the need to establish a "paper trail" which can be used in a court of law in case of lawsuit, often replaces the sensible, humane, personalized decision so important to proper caregiving.

Though many health professionals strive to build personal relationships of trust with their patients, the organizational requirements of today's health care system often make this very difficult.

Responsibility for Care

While individual autonomy is still the ideal, people live to older ages, a larger number become less able to care for themselves and make decisions about care towards the end of their lives. Traditionally, families have assumed the role of caregiver and decision-maker. However, society has become more mobile and as the number of broken families has increased, the ability of family to rally around a sick, elderly relative and consult with physicians, hospitals and nursing homes about care has lessened.

As the population ages, children of patients over 90 years of age are often themselves old and unable to take care of a sick parent without assistance. With an aging population, problems of dementia also increase, making the exercise of principles of autonomous decision making more complicated.

As a result, families are increasingly called upon to play a greater role in caregiving at the same time that distance and economic circumstances make it difficult for them to perform its role well.

The Rationing Debate : the Individual Versus the Community – the Old Versus the Young

Today, the propensity to treat with all reasonable available means is the norm unless a prior directive clearly indicates otherwise.

As health care costs have skyrocketed, many in America have raised questions bout whether care should indeed be rationed. They argue that we cannot afford to offer every technologically sophisticated test and procedure to all who desire them. Should we keep alive a comatose patient with very little hope of recovery at a cost of over $100,000 per year, they ask. Shouldn't we let that patient die and reapply the funds to those who cannot afford insurance?

An increasingly more common version of this argument pits the old against the young. Should we spend money on kidney dialysis for a frail 95-year-old? Wouldn't the money be better spent on providing better nutrition for pregnant women and newborn babies?

Many others believe that proving the best care possible to all (unless a prior directive clearly indicates otherwise) is the only appropriate moral stance. They argue that to do otherwise is to set oneself up as a judge of who should live or die, or even to engage in murder. They point out that pulling a feeding tube from someone causes that person to starve to death when food is available. Shutting off a ventilator causes asphyxiation when air is available.

An Ethics-Driven Health Care System

Thousands of individual decisions are made every day in the United States which implicitly apply ethical standards to health care. Too often these decisions are not guided by clear ethical guidelines which have been explicitly developed. As a result, many consumers and caregivers are left with uneasy feelings about values which underlie the way our health care system actually operates.

We have created a system where equality to health care does not exist.

For a system to be truly driven by explicit ethical standards, moral ideals must be established as goals, even if they cannot always be met to the letter in practice. These goals must address issues of equality of access to care, the degree to which trust should govern, who has the responsibility for care and for end-of-life decisions and whether care should be rationed based on economic or community goals. Our system does not do this today.

References

1. Schloendorff vs Society of New York Hospital, 322 NY, 1215, 105 NE 92, 95 (1914).
2. "Non-Terminal Patients and the Right to Die," Medical Ethics Advisor 7:4, April 1991, pp. 47-509.
3. Belkin, Lisa. "As Family Protests, Hospital Seeks an End to Woman's Life Support," New York Times. January 10, 1991.
4. New York Times. May 18, 1990.
5. Medical Ethics Advisor; op cit., pp. 47-50.

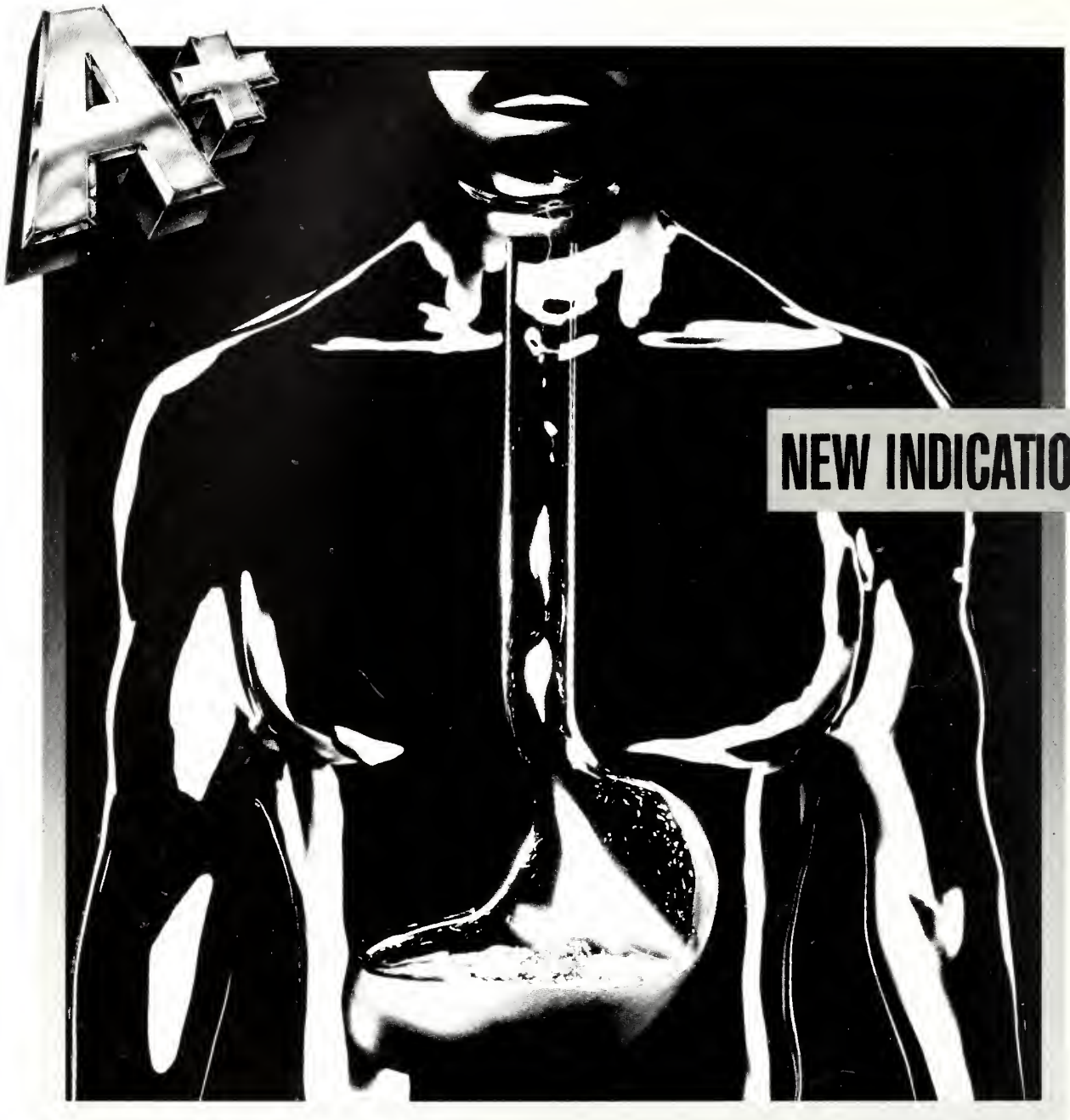
RHODE ISLAND COMPUTERIZED IMAGING, INC.

Cat Scan Facility
401•751•1110

weekdays
7 am - 5 pm

- Evening appointments for contrast studies
- Medicare, Ocean State
  Rhode Island Blue Cross/Blue Shield approved
- Board Certified Radiologist

Located in: Atwood Medical Center
Suite LL3
1524 Atwood Avenue
Johnston, RI 02919



ONLY ONE H_2-ANTAGONIST HEALS REFLUX ESOPHAGITIS AT DUODENAL ULCER DOSAGE. ONLY ONE.

Of all the H_2-receptor antagonists, only Axid heals and relieves reflux esophagitis at its standard duodenal ulcer dosage. Axid, **150** mg b.i.d., relieves heartburn in **86%** of patients after one day and **93%** after one week.[1]

AXID®
nizatidine
150 mg b.i.d.

ACID TESTED. PATIENT PROVEN.

AXID®

nizatidine capsules

Brief Summary. Consult the package insert for complete prescribing information.

Indications and Usage: 1. *Active duodenal ulcer*—for up to 8 weeks of treatment at a dosage of 300 mg h.s. or 150 mg b.i.d. Most patients heal within 4 weeks.

2. *Maintenance therapy*—for healed duodenal ulcer patients at a dosage of 150 mg h.s. at bedtime. The consequences of therapy with Axid for longer than 1 year are not known.

3. *Gastroesophageal reflux disease (GERD)*—for up to 12 weeks of treatment of endoscopically diagnosed esophagitis, including erosive and ulcerative esophagitis, and associated heartburn at a dosage of 150 mg b.i.d.

Contraindication: Known hypersensitivity to the drug. Because cross sensitivity in this class of compounds has been observed, H_2-receptor antagonists, including Axid, should not be administered to patients with a history of hypersensitivity to other H_2-receptor antagonists.

Precautions: *General*—1. Symptomatic response to nizatidine therapy does not preclude the presence of gastric malignancy.

2. Dosage should be reduced in patients with moderate to severe renal insufficiency.

3. In patients with normal renal function and uncomplicated hepatic dysfunction, the disposition of nizatidine is similar to that in normal subjects.

Laboratory Tests—False-positive tests for urobilinogen with Multistix® may occur during therapy.

Drug Interactions—No interactions have been observed with theophylline, chlordiazepoxide, lorazepam, lidocaine, phenytoin, and warfarin. Axid does not inhibit the cytochrome P-450 enzyme system; therefore, drug interactions mediated by inhibition of hepatic metabolism are not expected to occur. In patients given very high doses (3,900 mg) of aspirin daily, increased serum salicylate levels were seen when nizatidine, 150 mg b.i.d., was administered concurrently.

Carcinogenesis, Mutagenesis, Impairment of Fertility—A 2-year oral carcinogenicity study in rats with doses as high as 500 mg/kg/day (about 80 times the recommended daily therapeutic dose) showed no evidence of a carcinogenic effect. There was a dose-related increase in the density of enterochromaffin-like (ECL) cells in the gastric oxyntic mucosa. In a 2-year study in mice, there was no evidence of a carcinogenic effect in male mice, although hyperplastic nodules of the liver were increased in the high-dose males as compared with placebo. Female mice given the high dose of Axid (2,000 mg/kg/day, about 330 times the human dose) showed marginally statistically significant increases in hepatic carcinoma and hepatic nodular hyperplasia with no numerical increase seen in any of the other dose groups. The rate of hepatic carcinoma in the high-dose animals was within the historical control limits seen for the strain of mice used. The female mice were given a dose larger than the maximum tolerated dose, as indicated by excessive (30%) weight decrement as compared with concurrent controls and evidence of mild liver injury (transaminase elevations). The occurrence of a marginal finding at high dose only in animals given an excessive and somewhat hepatotoxic dose, with no evidence of a carcinogenic effect in rats, male mice, and female mice (given up to 360 mg/kg/day, about 60 times the human dose), and a negative mutagenicity battery are not considered evidence of a carcinogenic potential for Axid.

Axid was not mutagenic in a battery of tests performed to evaluate its potential genetic toxicity, including bacterial mutation tests, unscheduled DNA synthesis, sister chromatid exchange, mouse lymphoma assay, chromosome aberration tests, and a micronucleus test.

In a 2-generation, perinatal and postnatal fertility study in rats, doses of nizatidine up to 650 mg/kg/day produced no adverse effects on the reproductive performance of parental animals or their progeny.

Pregnancy—Teratogenic Effects—Pregnancy Category C—Oral reproduction studies in rats at doses up to 300 times the human dose and in Dutch Belted rabbits at doses up to 55 times the human dose revealed no evidence of impaired fertility or teratogenic effect; but, at a dose equivalent to 300 times the human dose, treated rabbits had abortions, decreased number of live fetuses, and depressed fetal weights. On intravenous administration to pregnant New Zealand White rabbits, nizatidine at 20 mg/kg produced cardiac enlargement, coarctation of the aortic arch, and cutaneous edema in 1 fetus, and at 50 mg/kg, it produced ventricular anomaly, distended abdomen, spina bifida, hydrocephaly, and enlarged heart in 1 fetus. There are, however, no adequate and well-controlled studies in pregnant women. It is also not known whether nizatidine can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. Nizatidine should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nursing Mothers—Studies in lactating women have shown that 0.1% of an oral dose is secreted in human milk in proportion to plasma concentrations. Because of growth depression in pups reared by treated lactating rats, a decision should be made whether to discontinue nursing or the drug, taking into account the importance of the drug to the mother.

Pediatric Use—Safety and effectiveness in children have not been established.

Use in Elderly Patients—Healing rates in elderly patients were similar to those in younger age groups as were the rates of adverse events and laboratory test abnormalities. Age alone may not be an important factor in the disposition of nizatidine. Elderly patients may have reduced renal function.

Adverse Reactions: Worldwide, controlled clinical trials included over 6,000 patients given nizatidine in studies of varying durations. Placebo-controlled trials in the United States and Canada included over 2,600 patients given nizatidine and over 1,700 given placebo. Among the adverse events in these placebo-controlled trials, only anemia (0.2% vs 0%) and urticaria (0.5% vs 0.1%) were significantly more common in the nizatidine group. Of the adverse events that occurred at a frequency of 1% or more, there was no statistically significant difference between Axid and placebo in the incidence of any of these events (see package insert for complete information).

A variety of less common events were also reported; it was not possible to determine whether these were caused by nizatidine.

Hepatic—Hepatocellular injury (elevated liver enzyme tests or alkaline phosphatase) possibly or probably related to nizatidine occurred in some patients. In some cases, there was marked elevation (>500 IU/L) in SGOT or SGPT and, in a single instance, SGPT was >2,000 IU/L. The incidence of elevated liver enzymes overall and elevations of up to 3 times the upper limit of normal, however, did not significantly differ from that in placebo patients. All abnormalities were reversible after discontinuation of Axid. Since market introduction, hepatitis and jaundice have been reported. Rare cases of cholestatic or mixed hepatocellular and cholestatic injury with jaundice have been reported with reversal of the abnormalities after discontinuation of Axid.

Cardiovascular—In clinical pharmacology studies, short episodes of asymptomatic ventricular tachycardia occurred in 2 individuals administered Axid and in 3 untreated subjects.

CNS—Rare cases of reversible mental confusion have been reported.

Endocrine—Clinical pharmacology studies and controlled clinical trials showed no evidence of anti-androgenic activity due to nizatidine. Impotence and decreased libido were reported with similar frequency by patients on nizatidine and those on placebo. Gynecomastia has been reported rarely.

Hematologic—Anemia was reported significantly more frequently in nizatidine than in placebo-treated patients. Fatal thrombocytopenia was reported in a patient treated with nizatidine and another H_2-receptor antagonist. This patient had previously experienced thrombocytopenia while taking other drugs. Rare cases of thrombocytopenic purpura have been reported.

Integumental—Urticaria was reported significantly more frequently in nizatidine- than in placebo-treated patients. Rash and exfoliative dermatitis were also reported.

Hypersensitivity—As with other H_2-receptor antagonists, rare cases of anaphylaxis following nizatidine administration have been reported. Rare episodes of hypersensitivity reactions (eg, bronchospasm, laryngeal edema, rash, and eosinophilia) have been reported.

Other—Hyperuricemia unassociated with gout or nephrolithiasis was reported. Eosinophilia, fever, and nausea related to nizatidine have been reported.

Overdosage: Overdoses of Axid have been reported rarely. If overdosage occurs, activated charcoal, emesis, or lavage should be considered along with clinical monitoring and supportive therapy. The ability of hemodialysis to remove nizatidine from the body has not been conclusively demonstrated; however, due to its large volume of distribution, nizatidine is not expected to be efficiently removed from the body by this method.

PV 2093 AMP [101591]

Additional information available to the profession on request

Lilly

Eli Lilly and Company
Indianapolis, Indiana
46285

NZ-2947-B-249304

© 1991, ELI LILLY AND COMPANY

OCEAN STATE
MEDICAL WASTE REMOVAL

SERVING PHYSICIANS, DENTISTS & VETERINARIANS

• Cultures & Stocks • Pathological Waste
• Human Blood & Blood Products • Used Sharps • Animal Waste • Isolation Waste
• Unused Sharps • Dental Chemicals

401-942-1142

2227R Plainfield Pike
Johnston, RI 02919

EPA APPROVED
LIC. #RID987474970

PHYSICIAN NEEDED

July 1, 1992

BC/BE
FAMILY PRACTICE/INTERNAL MEDICINE

Successful family practice group is seeking an additional physician for a satellite office. Basic guaranteed salary plus incentives and fringe benefits. An excellent, lucrative opportunity for an aggressive physician at no start-up costs.

Reply to

Box P
RHODE ISLAND MEDICINE
106 Francis Street
Providence, RI 02903

RIMS
Insurance Brokerage Corporation

Insurance Professionals serving Health Care Professionals.

We do it better!

- Because our purpose is to serve RI doctors and allied health care professionals.
- Because our staff has 15 years of solid experience in medical liability underwriting.
- Because our board of directors is composed predominately of doctors with the same problems, stresses and concerns as you.
- Because we support political action in matters of health care benefiting all Rhode Islanders.
- Because our bottom line is superior service.

Phone 272-1050 — ask for Shirley and
Learn How We Can Do It Better For You!

RIMS Insurance Brokerage Corporation
The Experts in Medical Liability Insurance

Now offering up to 2M/4M limits for select insureds.

Also offering workers' compensation.

RIMS Insurance Brokerage Corporation
One Hayes Street, Providence, Rhode Island 02908
Phone (401) 272-1050 FAX (401) 272-1051

The Recent Controversy over Breast Implants and Their Risks

Howard S. Sturim, MD, FACS

More than 500 scientific articles confirming the safety of breast implants have been published since the early 1960s when silicone implants were approved for use.

Media attention was focused on silicone breast implants in the fall of 1990 when a consumer activist group claimed that implanted silicone poses an increased risk of cancer. These claims were based on a laboratory study of rats that was demonstrated in hearings, called by a Federal Food and Drug Administration panel, to have little or no relevance to humans.

When assessing cancer risk, the crucial distinction between the experience of humans and laboratory rodents is often overlooked by those questioning the safety of breast implants. Since the first investigations into this issue were conducted in 1947, it has been repeatedly shown that laboratory mice and rats develop a rare sarcoma in response to the insertion of almost any type of smooth-surfaced material, including cellophane, metals and various plastics. The tumor developed by these rodents, a fibrosarcoma, is not equivalent to breast cancer in humans.

Howard S. Sturim, MD, FACS, is Associate Clinical Professor of Surgery, Brown University, Chairman, Division of Plastic & Reconstructive Surgery, Roger Williams Medical Center and Miriam Hospital, Staff Surgeon, Rhode Island Hospital, Providence, Rhode Island.

In the spring of 1991, Connie Chung hosted a segment on television concerning breast implants. Unfortunately, the program was poorly constructed and dedicated to sensationalism and presented the cases of three or four women who had poor results and complications resulting from the use of breast implants. Some of the women had had reconstruction of breasts removed for cancer and some of the patients had polyurethane-covered devices. The inference was that the use of breast implants was an unacceptable health hazard and terrible things happen to women who had them and that there was a high risk of cancer following the use of breast implants. Surgitek, a division of Bristol-Myers Squibb, which manufactures the polyurethane-coated implants was asked to participate in this program and refused. The public was never told why they refused; but, the reason was that they were given exactly 30 seconds of program time to respond to 15 minutes of accusations and felt they could not adequately represent their product.

The media was quick to pick up on this program, and other noted medical authorities such as Sally Jessy Raphael followed suit with programs of their own. The result was that a new element had been introduced in the treatment of women who have had successful implants placed and those who contemplated it. That element was fear.

Based on the data that have been collected from more than 27 years of clinical experience, as well as a large number of scientifically reliable studies, both the American Society of Plastic and Reconstructive Surgeons and the American Society for Aesthetic Plastic Surgery continue to believe that breast implants are as safe as any implantable medical device and are beneficial to the vast majority of properly-selected patients. More than 500 scientific articles confirming the safety of breast implants have been published since the early 1960s when silicone implants were approved for use.

In the only large national survey of women with breast implants conducted by Market Facts, Inc. of Chicago, a panel of 100,000 households chosen to represent the nation's consumer population was screened for the presence of women with breast implants. The findings, which are based on the responses of 592 women who have had their implants in place for an average of eight years, accurately reflect

the experiences of the majority of women who choose to have the devices inserted for cosmetic or reconstructive purposes. Ninety-three percent of the respondents said they were satisfied with the results of their breast implant surgery and 96% said they would definitely or probably choose to have the surgery once again.

Breast cancer is one of the most common malignancies in humans, afflicting one out of every nine women in the United States. Since an estimated two million women have breast implants, some overlap between the two populations is to be expected.

If silicone carried special dangers, people who have had pacemakers and plastic joints would have a higher than normal incidence of cancer.

Concerns about breast implants center on the silicone with which they are made. However, while all silicone substances shed very tiny amounts of material, they are generally recognized as safe. Tablets taken for indigestion contain silicone. Injections are made less painful by coating syringes and needles with silicone, so that with every shot extremely small amounts of silicone are injected into the body. In fact, everyone comes into contact with silicone every day in food, plastic and paper products, clothing, furniture and many medicines. If silicone carried special dangers, people who have had pacemakers and plastic joints would have a higher than normal incidence of cancer; and yet the development of any type of cancer in relation to foreign bodies has been seen very rarely in humans.

At no time during the past 27 years of implant use has there been any indication that breast cancer occurs at a greater frequency among implant-augmented women. In the only large national epidemiological study conducted to date involving 3,111 women in Los Angeles County, whose implants have been in place for an average of almost eleven years, the incidence of breast cancer among augmented patients has been shown to be no greater than in women who do not have implants.[1] These findings hold true as well for women in the study population who have had their implants in place for more than twenty years.

The presence of a breast implant does indeed make it more difficult to thoroughly examine a breast using mammography, especially when a woman has moderate or severe capsule contracture. However, although it has been documented that some breast tissue may be "masked" by the presence of implants, an actual case of late cancer detection due solely to the devices has not been documented. All sound, statistical evidence indicates that if proper examinations, using special techniques, are performed at the appropriate intervals, cancer diagnosis should not be delayed. Women with augmented breasts should be referred to radiologists who have the necessary skill and experience to perform special mammographic techniques required by the presence of implants. The two X-rays of each breast that are typically taken in routine mammography are insufficient for women who have had breast enlargement. Displacement of the implants by the radiologist and additional customized X-rays of the breasts are needed. Research continues in an effort to develop new types of radiolucent breast implants that will allow complete visualization of breast tissue.

Polyurethane-covered breast implants have been used for more than 20 years and have been shown to offer significant benefit: a dramatic decrease in the rate of capsule contracture, perhaps less than 5%. It is estimated that about 10% of the approximately two million women who currently have breast implants in place have polyurethane-covered devices. However, concerns have been raised that gradual breakdown of the polyurethane foam over time may produce a compound called 2,4-diaminotoluene (TDA) that has caused liver cancer in laboratory animals. There are no documented cases in humans attributable to the use of these devices; however, the manufacturer has voluntarily removed the devices from the market and recently announced that it is not going to manufacture them in the future because of the controversy that exists.

There are viable existing alternatives for women who continue to have doubts about silicone-gel implants despite the safety information provided by their physicians. One of these options is the use of saline-filled breast implants. This type of implant is a silicone rubber "balloon" that is filled at the time of surgery with a saline solution. Because saline is very similar to the natural body fluids, it is safely absorbed if the implant should leak. Although the old varieties of saline implants were prone to deflation, users of today's models claim rates as low as 1%.

In summary, there are approximately 100,000 breast implant procedures performed in the United States each year. The operation has proven to be safe, effective and reliable. It has been safely used for breast enhancement and breast reconstruction for almost 30 years. In November of 1991, a committee of the Federal Drug Administration approved the continued use of silicone breast implants.

On January 6, 1992, the FDA called for a 45-day moratorium on the use of silicone gel-filled implants. The American Society of Plastic and Reconstructive Surgeons was denied access to the information that was used in making this ruling. Saline-filled implants continue to be used for breast reconstruction or breast enlargement.

Unfortunately, the media has exaggerated and distorted facts. The result has been the unfortunate production of unfounded fear in patients who have successfully undergone this surgery through the years and in those who may be considering it in the future.

References

1 Deapen DM, Pike MC, Casagrande JT and Brody GS. The Relationship between Breast Cancer and Augmentation Mammaplasty: An Epidemiologic Study, Plastic and Reconstructive Surgery, 1986. 77:361-367.

Suicide in Newport County 1975-1989

William F. Hoffmann, MD

The suicide rates in Newport County are lower than comparable national and state rates.

Suicide is the eighth leading cause of death in the United States and the third most common cause of death (after accidents and homicides) in the 15-24 year old age group.[1] At one time, it was viewed as primarily a mental health problem; it is now viewed as a public health problem that can be prevented.

Newport County, located in Southeastern Rhode Island, is 107 square miles in area and is comprised of Aquidneck Island (made up of the city of Newport and the towns of Middletown and Portsmouth), Conanicut Island (made up totally of Jamestown), and Tiverton and Little Compton, towns that lie to the east of the Sakonnet River and border on Massachusetts. In the 1980 census,[2] the county was 82% urban and 18% rural. The population of Newport County in the preliminary 1990[3] census was 87,194 with 64,544 on Aquidneck Island, 4,999 on Conanicut Island, and 17,651 in Tiverton and Little Compton. The population is 97% white and predominantly of the Catholic faith.

William F. Hoffmann, MD, is Clinical Assistant Professor of Psychiatry and Human Behavior, Brown University, and President-Elect, Rhode Island Psychiatric Society. He is in private practice in Middletown, Rhode Island.

Materials and Methods

Statistics used in this study were compiled by the Department of Vital Records of Rhode Island for the years 1975 through 1989, as well as US census figures of 1970, 1980 and preliminary figures for 1990. Only residents of Newport County are reported upon in this paper. Rates for suicide are given per 100,000 population. The total number of suicides was analyzed to examine the effects of age, sex, residence and method of suicide upon the suicide rate. Causes were coded according to the International Classification of Diseases (ICD-9), and comparisons are made with Rhode Island and national statistics when appropriate.[3,4]

Newport County residents who committed suicide in other states were included in the total number of suicides. Because of confidentiality issues and record-keeping difficulties in five states, the age, sex and method of suicide were not available for seven suicides.

Results

The total number of suicides from 1975 to 1989 was 127, for a rate of 10 per 100,000 population. This is broken down to 50 deaths from 1975 through 1979 (rate 12.5 per 100,000), 37 deaths from 1980 to 1984 (8.3 per 100,000), and 40 deaths from 1985 through 1989 (10 per 100,000). The suicide rates in Newport County are lower than comparable national and state rates (Figure 1 and Table 1).

Racially, there were only two non-white suicides in the 15 years, both in the 1980-1984 period. This comprised 1.6% of the total number of suicides, compared to 3% non-white suicides from 1985-1988 in Rhode Island (Table 2).

Sixty-three percent of the suicides were male. The percentage of males increased during the three periods examined from 52% in 1975-1979 to 77% in 1985-1989. From ages 10-44, 79% of the suicides were male, but after age 44, 57% of the victims were female. Recent Rhode Island statistics differ somewhat from these statistics in that from the year 1985-1988, 80% of suicides under age 45 were male and after age 45, 66% of the suicides were also male (Table 3).

The incidence rate of suicide increased with increasing age, as seen in Table 4. The incidence rate of teenage suicide and suicide in the young (ages 10-24) is generally low. The incidence rate of 7.8 per 100,000 suicides in the 10-24 age group is lower than the

national (10.1) and Rhode Island (9.5) incidence rates from 1985-1988. The breakdown of this incidence reveals that in the 13-19 age group, the Newport County suicide rate is very low, (4.5) nearly half the national (9.2) and Rhode Island (8.5) rates. It is higher, however, in the 20-24 age group (12.5). The increasing incidence of suicide through the life cycle in Newport County residents is consistent with national findings, but contrary to overall statistics in Rhode Island where there is a higher incidence rate in the 25-34 age group (17.6) with a generally diminishing incidence as individuals grew older.

The incidence rate of suicide increased with increasing age. . .

The method of suicide is summarized in table 5. The most common means of death was firearms, used 26% of the time, with hanging (20%) and overdose (16%) each somewhat less than the Rhode Island averages, but this follows the same overall pattern seen both state-wide and nationally. An exception is the 14% death by drowning which is considerably above the state and national incidences and can be explained on the basis of the special geographic features of the Newport County area.

Table 1. **Suicides: Residents of Newport County 1975-1989**

Dates	Number	Rate/100,000
1975-1979	50	12.3
1980-1984	37	9
1985-1989	40	9.5
1975-1989	127	10
United States 1985-1988		12.6
Rhode Island 1975 - 1989		11.4

The residence of the victims is summarized in Table 6. Newport, as would be expected, being the most densely populated area, had the highest number of suicides (51) and Little Compton with the smallest population had the least (7). However, the rates per 100,000 show that less populated, more rural areas such as Jamestown and Little Compton experienced higher suicide rates than the more populated urban communities such as Newport, Middletown and Portsmouth.

Discussion

The overall suicide rate during the years studied is lower in Newport County than in Rhode Island or the United States. Though the numbers are small and inconclusive, we can hypothesize that Newport County's relative isolation and adherence to traditional values plays a role in the lower rate of suicide.

The high suicide rate from 1975 to 1979 (12.2) should be examined more closely. It barely exceeded the national rates (11.9) and was similar to the Rhode Island rates from 1975 to 1979 (12.4). Newport County in the mid and later 70s was experiencing considerable economic dislocation

Figure 1.

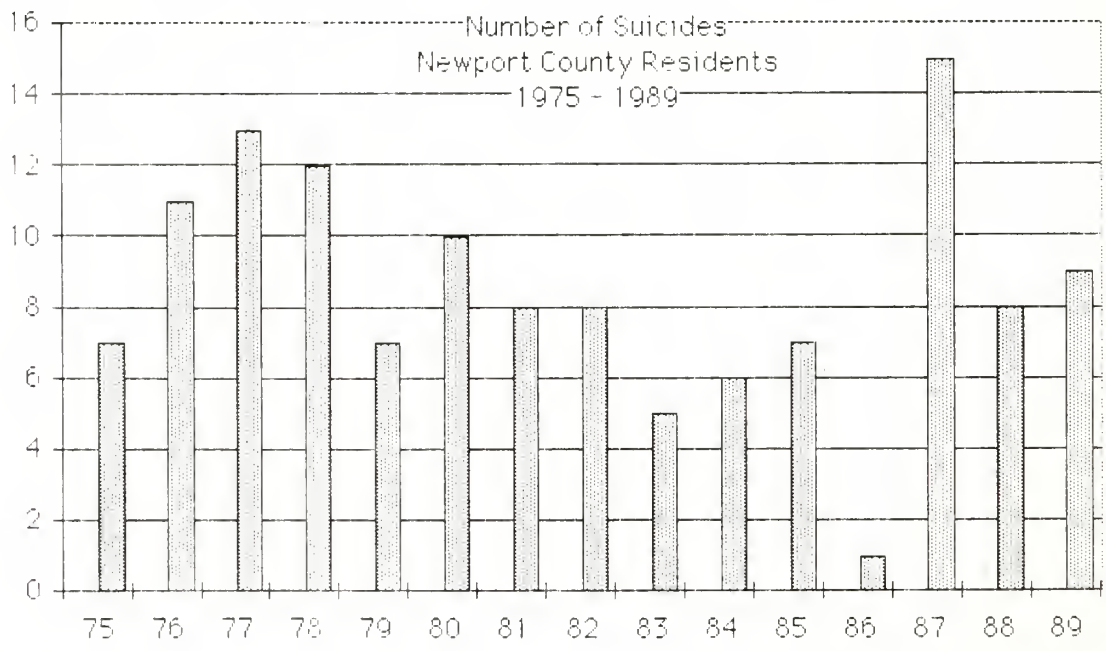


Table 2. **Race of Suicides**

Year	Race
1975-1979	100% White
1980-1984	94% White
1985-1989	100% White
1975-1989	98% White

Table 3. **Sex/Age Comparisons 1975-1989**

Years	Percentages	
	Male	Female
1975-1979	52%	48%
1980-1984	64%	36%
1985-1989	77%	23%
1975-1989	63%	37%

Age Group*	Male	Female
10-44	50 (79%)	13 (21%)
45-75	25 (44%)	32 (56%)

*Seven suicides committed in other states are not included in these data.

Table 4. **Number of Suicides by Age Group***

	10-24	13-19	20-24	25-34	35-44	45-54	55-64	65-74	75+
1975-1979	10	2	8	6	8	5	8	9	0
1980-1985	5	1	4	7	6	9	3	2	4
1985-1989	8	4	4	8	5	5	5	4	3
Incidence per 100,000	7.8	4.5	12.5	10.4	13.2	16.3	14.2	17.3	12.4

* Seven suicides committed in other states are not included in these data

Table 5. **Method of Suicide***

Years	Overdose	Inhalation	Hanging	Jumping	Drowning	Gunshot	Cutting	Other
1975-1979	18%	14%	12%	4%	22%	27%	0	3%
1980-1984	9%	9%	29%	6%	15%	15%	9%	8%
1985-1989	22%	17%	23%	0	0	38%	0	0
1975-1989	16%	12%	20%	8%	14%	26%	2%	2%

* Seven suicides committed in other states are not included in these data.

Table 6. **Numbers of Suicides by Townships**

	1975-1979	1980-1984	1985-1989	Total #	% of Total	Rate/100,000
Jamestown	5	2	5	12	9.4	18.6
Little Compton	5	2	2	9	7	19.3
Middletown	8	4	4	16	12.5	6
Newport	18	20	15	53	42	12.2
Portsmouth	9	7	9	25	19.7	11
Tiverton	5	2	5	12	9.4	6

because of a reduction in Navy forces resulting in a population decline of 17% from 1970 to 1980. Suicide rates rise during periods of economic hardship; it can be hypothesized, therefore, that these difficult economic conditions contributed to the unusually high suicide rate in Newport County seen for those years.

Suicide is committed predominantly by white males, in Newport County as elsewhere, but the higher percentage of female suicides above age 45 (57%) differs considerably from the national and state findings (approximately 33%).

Suicide rates rise during times of economic hardship.

The low suicide rate amongst teenagers is worthy of further attention. Though extremely low from 1975 to 1984 (2.9), it increased from 1985 to 1989 (7.9) and approached, but did not equal, state and national levels during the late 80s. Though these figures are mixed and inconclusive, it suggests that factors such as the isolation of Newport County, its adherence to traditional values and the structure of schooling during teenage years may have exerted a protective effect. The consistently higher incidence of suicide in the 20-24 age group (12.4) suggests an increased vulnerability in this age group and various socioeconomic factors might be operative.

The highest suicide rate is found in the 65-74 age group, and in general, the suicide rate increases with age in Newport County. This suggests the possibility of an increasing suicide rate in the 90s as the population ages. However, this trend was not noted during the 80s when compared with the latter half of the 70s.

The residency figures show that the least-densely populated and most isolated communities in the county – Jamestown and Little Compton – had the highest suicide rates. Other community suicide rates were more reflective of overall county and state averages with the exception of Tiverton and Middletown which were quite low. The City of Newport, it should be noted, was the only area in Newport County to how an increase in the rate of suicide in the 80s as compared to the latter half of the 70s. The city of Newport is the most densely populated area and has the highest number of individuals in the 24-34 age group. This group had the highest number of suicides, though the overall incidence was not especially high, and considerably lower than the Rhode Island rate of 1985-1988.

In terms of programs designed to reduce suicide rates, the data suggest that outreach to the more isolated communities and the older population is needed. Younger males, particularly in the 20-24 age group, need our attention, and will continue to be a high risk group particularly in the light of a failing economy. Educational efforts highlighting the risks of drug and alcohol abuse which have been shown to be associated with suicide in young people in Rhode Island,[5] as well as education regarding psychiatric illness, such as depression, panic disorder and schizophrenia, often associated with suicide,[6] also need to be emphasized.

References

1. The National Center for Health Statistics, 1990. The Health of the United States in 1988, DHHS Publication #91-1232, Washington, DC. US Government Printing Office.
2. 1980 Census of Population, Vol. 1, Chapter B, Part 41. Rhode Island, US Department of Commerce, Bureau of the Census, March 1982.
3. *The Providence Journal*, February 18, 1991 p A-3.
4. Suicide in Rhode Island: Patterns and Trends, 1985-1988. A Health Statistics Report; Rhode Island Department of Health, Office of Health Statistics. April 1989.
5. Sturner, William Q. Adolescent Suicide Fatalities. *Rhode Island Medical Journal* October 1986, Vol. 69, pages 471-475.
6. Maltsberger, John T. 1986, Suicide Risk. New York: New York University Press.

Address correspondence to:
William F. Hoffmann, MD
294 Valley Road
Middletown, RI 02840

PSYCHIATRIST

Brown University Dept. of Psychiatry
Affiliated Program

Currently recruiting for Medical Director of Partial Hospitalization Program. For this exciting new program, the position requires a Board Eligible or Board Certified Psychiatrist for 20 hours per week, Massachusetts License required. Health benefits and a Brown appointment are possibilities for the right candidate. Interested applicants please contact:

James Reich, MD
Associate Medical Director
Corrigan Mental Health Center
49 Hillside Street
Fall River, MA 02720

(508) 670-2901
Monday through Friday, 9 am to 5 pm

Are your investments as successful as you are?

*I*f your hard work and success have allowed you to build a portfolio of $250,000 or more, we'd like to work with you.

account administrator who will act as your personal financial advisor and you'll be backed by a team of investment managers with a history of proven investment success.

[*Professionally Managed Investments*]

Because at Citizens Bank, our Trust and Investment Management team can provide you with the exceptional service, experience, and performance that will help you get the most from your investments. You'll have an

To put us to work for you call Malcolm Starr at 456-7445. Because there's never been a better time for Citizens.

Trust and Investment Management Services

CITIZENS BANK

Citizens Trust Company/Citizens Savings Bank

HEALTH BY NUMBERS

Rhode Island
Department of Health
Barbara A. DeBuono, MD, MPH
Director of Health

Elder Suicide in Rhode Island

Among Rhode Islanders aged 65 and over, suicide is the third leading cause of injury death following falls and motor vehicle crashes.[1] During the period 1984-1988, the suicide rate in this group (12.6 per 100,000 per year) was slightly lower than the rate for Rhode Islanders aged 15-64 (14.7), and substantially lower than the 1986 national rate for elders of 21.5[2] (Figure 1). Rhode Island suicide rates for those aged 15 and over ranged from a low of 11.5 for ages 55-64 to a high of 19.6 for ages 25-34. Nationally, the highest rate for any age group was found among the elderly.

From 1984-1988, there were 88 elder suicides (65 men, 23 women). The corresponding rates (24.3 and 5.3 per 100,000 respectively) illustrate that elderly men are at much higher risk of suicide than elderly women. Among men, the suicide rate increased with age through the 85-89 age group (Figure 2); due to small numbers, age trends among women could not be detected. The age pattern for men is consistent with the hypothesis that elder suicide is motivated by disease and disability. However, more information is required on the circumstances of each case to investigate causality.

The risk of suicide is significantly related to marital status. During 1984-1988, the age- and sex-adjusted suicide rate of unmarried (divorced, widowed, or never married) elders was 2.4 times the corresponding rate for married elders ($p < .05$). The magnitude of this relative risk is consistent with national data.

Table 1 illustrates the methods of suicide utilized. Among those aged 65 and over, hanging was most prevalent, in contrast with those aged 15-64 who most often used firearms. While more elderly male suicides involved firearms (29%) than any other method, no elderly women selected this method. The method most frequently selected by elderly women was inhalation of motor vehicle exhaust (39%). Nationally during 1980-1986, firearms were the most common method for both elderly men (73%) and women (29%); poisoning (26%) and hanging (20%) were also common for women. The difference in proportion of firearm suicides for Rhode Island and the US is statistically significant for both elderly men ($p < .001$) and women ($p < .01$).

Suicide continues to take the lives of many elderly Rhode Islanders each year. By studying the profile of these victims, high risk groups can be identified and targeted preventive measures may be designed.

References

1 Zimmerman H, Goulet R. A Compendium of Rhode Island Injury Mortality Data, 1979-1988. Providence, RI: RI Department of Health 1990.

2 Meehan P, Saltzman L, Sattin R. Suicides Among Older United States Residents: Epidemiologic Characteristics and Trends. *American Journal of Public Health*, 1991; 81:1198-1200.

Table 1. **Number and Percentage Distribution of Suicides b y Method and Gender, Rhode Island Residents, Ages 65 and Over, 1984-1988**

	Total		Male		Female	
Method of Suicide	No.	%	No.	%	No.	%
Hanging	21	23.9	18	27.7	3	13.0
Firearm	19	21.6	19	29.2	0	0.0
MV Exhaust Inhalation	14	15.9	5	7.7	9	39.1
Poisoning	13	14.8	7	10.8	6	26.1
Submersion/Drowning	9	10.2	5	7.7	4	17.4
Sharp Object	6	6.8	5	7.7	1	4.3
Other	6	6.8	6	9.2	0	0.0
Total	88	100.0	65	100.0	23	100.0

Submitted by the Injury Prevention Program, Ann Thacher-Renshaw, Project Director, Thomas Largo, Project Epidemiologist.
Health by Numbers *is edited by Jay S. Buechner, PhD, and William J. Waters, Jr, PhD.*

Figure 1. **Suicide Rates for Rhode Island Residents, 1984-1988, and the US 1986, for ages 15-64 and 65 and Over**

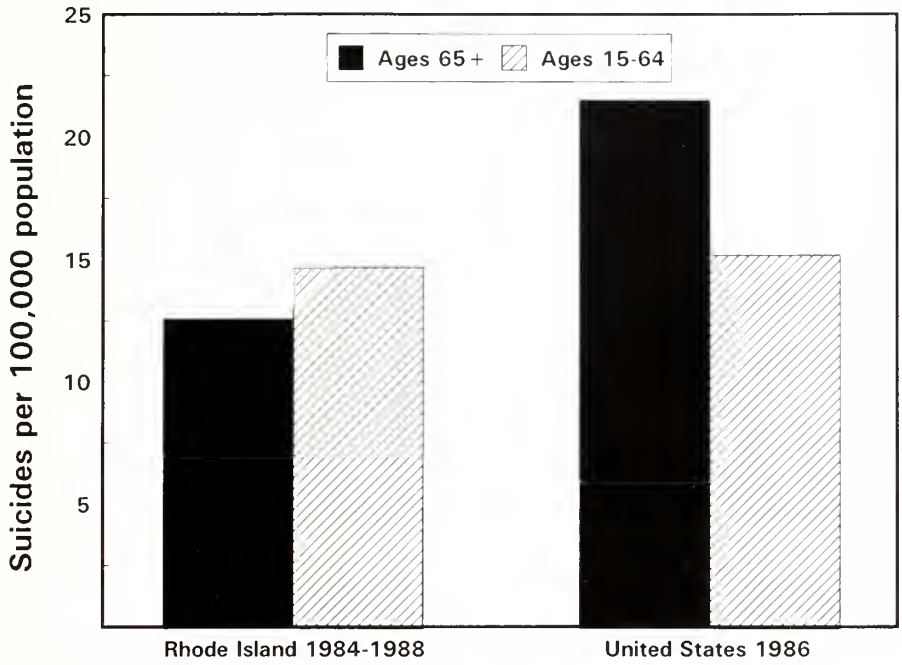
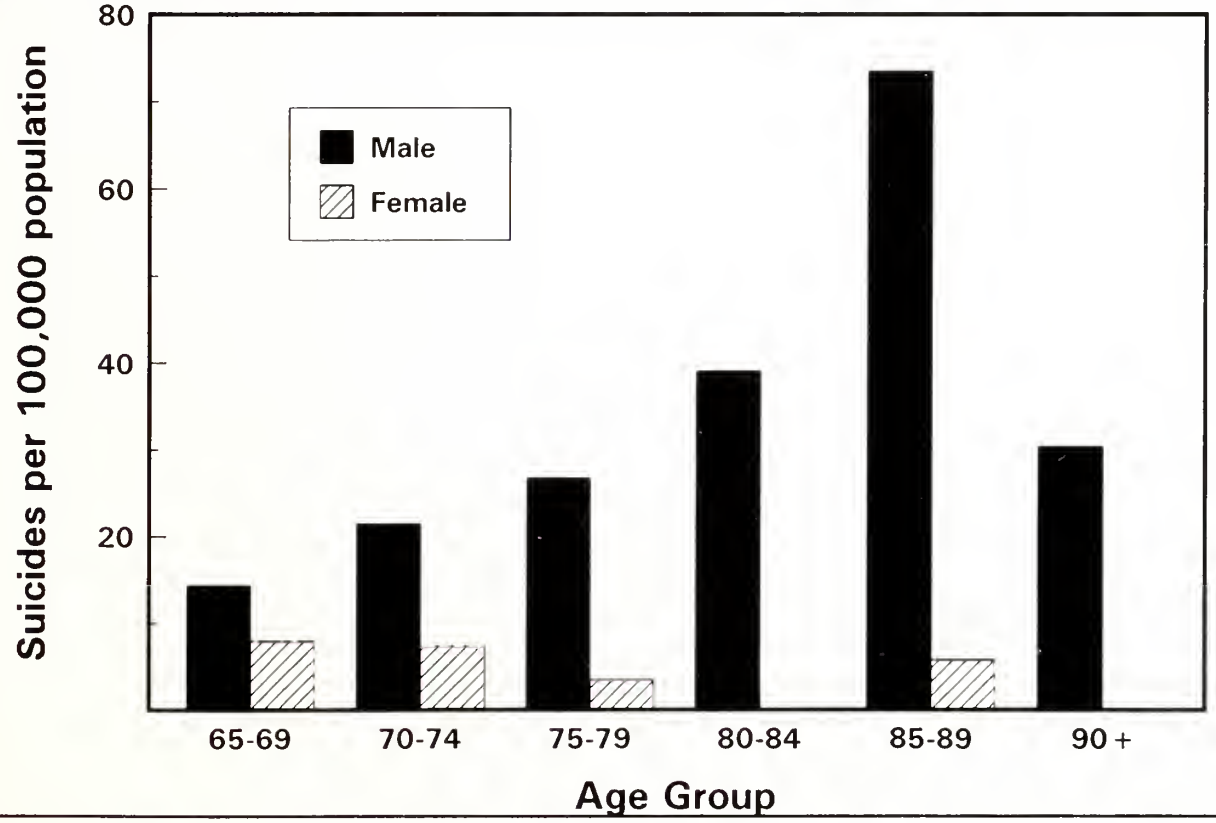
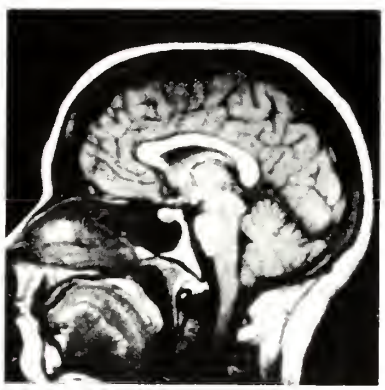


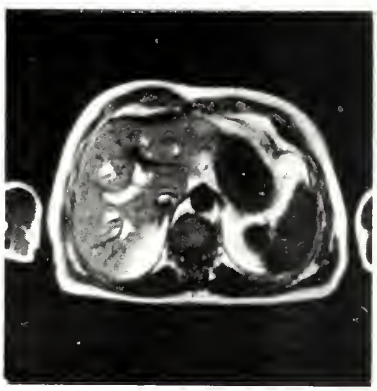
Figure 2. **Suicide Rates for Rhode Island Residents, ages 65 and Over, 1984-1988, by Age and Gender**



RI-MASS MRI, P.C. is pleased to sponsor the

2ND WEDNESDAY LECTURE SERIES





WHEN: The 2nd Wednesday
of each month
6:30 p.m. - 7:30 p.m.

WHERE: Marriott Hotel
Charles at Orms
Providence, RI 02904

THIS MONTH'S TOPIC:
"Imaging of the Central Nervous System in AIDS"
Wednesday, March 11, 1992

NEXT MONTH'S TOPIC:
"MRI of Cerebral Vascular Disease"
Wednesday, April 8, 1992

TO REGISTER/CALL: 1 (800) 848-9661

For certain categories of taxpayers, we are still accepting contributions that will be deductible for 1991.

THE NEWLY APPROVED MEDICAL ASSOCIATION TRUSTS
(Summit Bancorporation, Trustee)
(CoreStates Bank, Trustee)

* V.E.B.A. PLAN

FEATURES

UNLIMITED TAX DEDUCTIBLE CONTRIBUTIONS

REGARDLESS OF YOUR PENSION SITUATION

AND IS NOW

IRS APPROVED FOR USE BY DOCTORS IN OTHER STATES

EVEN IF . . .

- YOUR PENSION PLAN IS OVER FUNDED
- YOUR PENSION PLAN IS MAXIMUM FUNDED
- YOU HAVE NO PENSION PLAN

PLEASE SEND ME A copy of the I.R.S. "Favorable Letter of Determination" and other relevant information on your *V.E.B.A. Plan

NAME _____

ADDRESS _____

DATE OF BIRTH _____ TELEPHONE # (____) _____

Mail to: THE KIRWAN COMPANIES
402 MIDDLETOWN BLVD., SUITE 202
LANGHORNE, PA 19047

(800) 969-7666 ..... (215) 750-7616 ..... FAX (215) 750-7791

*VOLUNTARY EMPLOYEE BENEFITS ASSOCIATION

NURSING PLACEMENT
HOME CARE INC.

"The 1st Choice in Certified Home Health Agencies"

We Are Proud To Announce:

NURSING PLACEMENT HOME CARE, INC.,
a **MEDICARE** and **MEDICAID CERTIFIED AGENCY.**

NPHC, the only letters that define Quality and Dependable Home Health Care in RI. Your patients deserve a choice and **NPHC** can offer them that – with a complete range of care options from Home Health Aides to Registered Nurses and all therapies.

We have provided your hospitals and private patients with quality care for 15 years and are now certified to serve all homebound patients in Rhode Island.

- RN assessments
- 24 hr. supervision
- RN
- HHA
- PT
- OT
- Speech
- MSW
- IV Therapy
- Pediatrics

"For Home Care You Can Rely On"

NPHC

Please call 453-4474
1-800-287-2940

Doctors, Drug Companies and Gifts: Some Local Views

In the December, 1991 issue, this journal carried a paper by Chren and Landefeld entitled *Doctors, Drug Companies and Gifts*. Their article expressed concern that the commercial interests of the pharmaceutical industry were in conflict with the ethical standards of the medical profession, particularly through drug company gifts to physicians and the underwriting of hospital-based conferences. While acknowledging that companies have a right to promote their products, they concluded, " . . . as individuals, physicians should avoid accepting gifts from drug companies. Patients' money is spent unfairly. Gifts may threaten the physician-patient relationship by altering our prescribing practice. Gifts may also shift the balance between altruism and self-interest in our professional lives."

The editors have asked a number of Rhode Island's practicing physicians to express their personal views on this issue. Their responses follow.

The article *Doctors, Drug Companies, and Gifts* by Drs Chren and Landefeld (*RI Medical Journal*, December 1991–Vol. 74) very clearly laid out the ethical problems associated with gifting and gift-receiving in the profession.

The drug company uses gifts to amplify its sales and income. The costs are considered business expenses and are deductible from taxable income. The recipients of these gifts (meals, trips, trinkets etc.) are not taxed on the value of these gifts up to certain amounts. So the appearance is very legal and proper in the eyes of the IRS.

The ethical problem is not universal. In a business venture the goal is to "make a profit, no matter how" as long as the enticements to buy your product do not break any laws or bend the truth too far.

A different standard of ethical behavior is applied to the physician whose goal is not to make money "no matter how" but to do the best for the patient. He/She must not give the impression of making a profit from the misfortune of the sick person. He/she must behave in a manner that is free from any taint of greed, or the suggestion of "let the buyer beware."

The behavior of bankers, architects, lawyers, engineers, manufacturers, retailers, professional athletes, and captains of industry is considered unethical when applied by physicians. How saintly we must be.

Herbert C. Lichtman, MD
The Miriam Hospital

• • •

It is always a relief to see that other physicians are as disquieted about pharmaceutical company gifts as I am. We have, I think, come a ways since angry medical students were hurling Lilly stethoscopes off piers or mailing them to Hanoi (my own 1983 medical school class was sharply divided about them; I recall some sent them to third world clinics), but I am hopeful that we have dispensed more with the showy displays of anger than with the discomfort. Chren and Landefeld reiterate the important point that is central to all discussions of this topic, which is that when we physicians prescribe medication, we are not spending our own money, but someone else's. Like members of Congress, our relationships to organizations who stand to profit by our actions merit scrutiny.

Consequently, I have no quarrel with the thrust of their discussion. I would comment on a couple of points, however. First, the early parts of Chren and Landefeld's article moves back and forth a bit too casually between drug marketing and gifts–related but not identical issues. The $5 billion spent in drug marketing (I assume the number is correct) sounds outrageous, but the choice is not between drug ads or gifts and the salaries of 50,000 clinical pharmacologists; it is between using a competitive marketplace or a centrally planned economy to drive the development and production of drugs. The economic distortions of the medical marketplace notwithstanding, competitive market economies are supposed to create efficiency and innovation and a case can be made that in the pharmaceutical industry, warts and all, this occasionally happens. That $5 billion is arguably part of the cost of the system that drives the development of new growth factors, antibiotics and anti-anginals, some of which are genuine improvements in how we care for our patients. Put another way, the money spent marketing soap, beer and automobiles could also be spent on socially more desirable ends. But to say that we would invariably be better off ignores the deeper economic issues that eliminating these costs would raise. Chren and Landefeld may indeed feel social justice mandates that the phar-

maceutical industry should not be part of a marketplace – a case for this can indeed be made – but unless they are willing to confront this very tangled issue head on, I think they are obliged to temper their indignation.

As for me, I am not quite ready to overthrow the system yet. The important issue is not marketing, but sleaze. If propoxyphene and cerebrovasodilators are being misrepresented, then those doing so should be held accountable for misrepresentation as should physicians who substitute knowledge of advertising claims for genuine expertise.

The deeper question raised by Chren and Landefeld is the role of gifts within the marketing strategy of pharmaceutical firms. As a former student of comparative religion, though not of Mauss specifically, I appreciate the attempt to locate what is taking place here in a much broader cultural context. Mauss's work represents part of a critical departure of 19th century thought that sought to explore the unconscious content and themes of various forms of "primitive" behavior and cultural activity, seeing in such cultures a kind of dream like world untransformed by modern scientific rationalism. Primitive culture was another "royal road" to the unconscious, a kind of cultural dream canvas unmarred by industrial soot. Contemporaries of Mauss, such as Emil Durckheim and Sigmund Freud trod the same ground, with equally fascinating results. More recently, Norman O. Brown, in his remarkable essay on the psychoanalytic symbolic content of modern economic behavior, has extended Mauss's insight on the universality of the gift relationship to include the unconscious symbolism of guilt and debt (in German, both = *schuld*). These are deep waters indeed and they need to be navigated with caution, but they are entered of necessity with the claim that Mauss's pygmies instruct modernity.

In fact, most physicians I think do feel a debt in response to drug company gifts that is usually repaid as time – time to listen to a sales pitch, review some marketing material or develop a relationship with a company "rep" that encourages freer access to the office. Most observers seem comfortable at this low level of exchange.

But it is again the fact that we are spending other people's money, not our own, that threatens to slide our interaction with the pharmaceutical industry into relationships that I suspect Mauss did not describe – ie, the "bribe relationship" or the "kickback relationship". This point was driven home recently when the manufacturer of an anti-hypertensive agent offered "frequent flyer" bonuses to physicians according to how much was prescribed. Observers disinclined to dither over the niceties of "gift" relationships had no trouble labelling this marketing strategy as a kickback.

An analysis such as Mauss's reminds us that gift relationships have meaning within a culture, and to the extent that they are under scrutiny, those involved need to recognize how observers in the culture are going to interpret the actions. Patients and the public have a right to feel reassured that they can trust us as advocates and that we are not beholden to interests (including our own) that stand to profit by their misfortune. In other realms of public service, the standard is to avoid even the appearance of being influenced – a measure of the power of cultural perceptions of gift relationships. While recognizing that the distinction between gift and "educational support" often gets very blurry, is that an unreasonable standard in our day to day interactions with the companies that stand to profit from our decisions?

Peter Rintels, MD
Rhode Island Hospital

• • •

Drs Chren and Landefeld have displayed an admirable degree of logic and tact in examining the relationship between the pharmaceutical industry and physicians, a relationship that can be conceived of as one wall in the edifice that is our health care system. It is indeed chilling to contemplate the fact that drug companies spend 5 billion dollars each year to influence our prescribing practices. The intent of this promotional barrage extends beyond convincing us of the superiority of one product over another. Rather, as with the great Cola Wars (ie, Pepsi vs Coke), the purpose is to convince us that consumption itself is important irrespective of the product.

Early in our medical training, we are indoctrinated in the use of drug samples in the ambulatory care setting. On the surface, pharmaceutical industry philanthropy enables us to provide our less well-off patients with "free" medication. However, simultaneously, and without fanfare, we become adept at dispensing drugs to patients with non-specific abdominal complaints, headaches, musculoskeletal discomfort, anxiety, depression, and a host of other symptoms without questioning the scientific merit or appropriateness of such therapy. Our patients get better, another drug has been added to our armamentarium, and just as we begin to reestablish our bearings, a new pharmaceutical agent is introduced to the sample closet. And the circle turns. Is it any wonder, then, that we are ill-equipped to counsel primary prevention, are uncomfortable with non-pharmacologic therapeutic options, and are faced with patients who truly believe nothing can be accomplished without a prescription?

While I agree entirely with Chren and Landefeld's analysis, I would emphasize different aspects of the issue, and consequently, would reach different conclusions. First, the gifts physicians receive for their own personal use can be easily identified and eliminated, and I believe, are of overall little importance. The greater challenge lies in our finding a way to refuse the drug samples we currently accept on behalf of our patients. Second, while the authors suggest that our acceptance of personal gifts from drug companies threatens both society's perception of our profession and the integrity of the physician-patient relationship, I believe there are threatening forces of far greater magnitude that are closer at hand. Specifically, although we are among the highest

paid of Americans, we invest in health care facilities, trivialize disease prevention, close our practices to welfare patients, and most disturbingly, lobby strenuously against legislative efforts to develop a workable system of universal access to health care.

Sadly, we have earned the unenviable distinction among industrialized nations of failing to guarantee health care to all our citizens, a distinction we now share only with South Africa. Our stance has become even more indefensible as of June when the Congressional General Accounting Office reported that " . . . if the United States were to shift to a system of universal coverage and a single payer, as in Canada, the savings in administrative costs would be more than enough to offset the expense of universal coverage." A national health program or even a national health insurance system would free us from the need to accept drug samples from the pharmaceutical industry. This is not to say that guaranteed health care would necessarily eliminate the practice of gift-giving and its attendant problems. Nor would it eliminate the widening gap in life expectancy between rich and poor that has been observed even in those countries with national health systems. Rather, as in Britain, Sweden and Canada, the issue of drug company gifts to physicians would continue to evoke lively debate but the professional and societal ramifications would be far less.

According to Chren and Landefeld, in establishing a gift relationship with drug companies, we foster injustice, that is an " . . . (un)fair allocation of burdens and benefits." On the other hand, the authors tell us that drug companies have a " . . . right to promote their products." Do the authors really believe this right is inviolable? Returning to my original analogy, have they identified a supporting wall, the removal of which will endanger the stability of the whole edifice? I believe it is more likely that the issue of pharmaceutical industry gifts to physicians for personal use is a cosmetic wall, the removal of which will change the look but not the structure. And, oh, do we need to change the structure.

David G. Kern, MD
The Memorial Hospital of
Rhode Island

• • •

The article by Drs Chren & Landefeld helps to address an issue which we have all been conscious of since medical school, but is rarely discussed in clinical practice. As such, this article is an important contribution to physician education and ethical standards.

My own experience is typical of what is described: The start of the "gift relationship" in medical schools with the presentation of stethoscopes, through textbooks as a resident, up to and including an offer for a weekend stay at the Waldorf-Astoria Hotel for a special conference on a newly-developed antidepressant medication (a "gift" that might have been accepted if my brother was not to be married on the same weekend). The article addresses the rights of drug manufacturers to market their products but I feel that the trinkets that are discussed at length in the article are really not the problem faced by physicians. It is not until towards the end of the article that Chren & Landefeld get to the particularly troublesome aspects of gifts: their linkage to "special" medical education for practicing physicians, the special nature being that which the pharmaceutical companies are trying to market.

I do not believe that there are many physicians who have truly been influenced to prescribe one drug over another because of pens, note pads, keychains, or friendly handshakes and smiles given in hospital corridors. I do believe, however, that the busy practicing physician can be led down the wrong road with the presentation of scientific material, most from reputable journals and authors, but taken out of context, perhaps not attached to an editorial in the same journal presentation of other facts from another author or linked to any possible follow-up studies. The trinkets are not the problem; the pseudo-education that one can get from the drug company representatives, whatever their education, remains, I believe, the real difficulty in marketing of drugs. The trinkets are a key, perhaps, to opening the physician's door, keeping the name of the product or manufacturer on his or her desk or that of the secretary's. I do believe that busy physicians can truly be influenced by a skewed series of articles or special compendium of studies handed to him after the representative is in the door.

I do see pharmaceutical representatives and will continue to see them. I do accept gifts from them, although continue to limit such to the pens and papers, and more importantly, samples of medications which, I believe, do in fact, help some of our patients by easing the cost of their medical bill through the free samples. I would encourage my fellow physicians, however, to go beyond whatever paper, lecture, book, or presentation is given them by whatever pharmaceutical representative and harken back to their own scientific training and the need to balance any studies that they have read with a critical eye and careful follow up self-education.

Daniel S. Harrop, MD
Butler Hospital

• • •

The article by Chren and Landefeld is timely and informative. The size of the financial commitment of the drug industry to marketing is astonishing. The evidence that drug companies affect physicians' prescribing behavior in ways which are contradictory to available state-of-the-art is dismaying.

It is all around us, often in subtle guise! Advertisements hang out of residents' coat pockets on pens, rulers, plastic pocket protectors, and stethoscopes. A bag which I use to supplement my briefcase has an instrument company logo on it. I recently attended a Grand Rounds given by a distinguished former colleague who basically gave a drug pitch. Two weeks

later I discussed that event with another former colleague just before he gave his Grand Rounds. Nonetheless his talk proceeded to emphasize a drug marketed by the drug company which supported him and after the talk, he allowed that he hoped it wasn't obvious. Indeed it had been subtle, which it could be argued, was worse than the more obvious drug pitch.

In all of these cases, it is difficult to fault the drug company or the physician. Nonetheless, stepping back and looking at the aggregate, I am concerned about the effect of these interactions on the integrity and image of the medical profession.

What can be reasonably done to improve the situation? It may help simply if we are aware, through presentations such as that of Chren and Landefeld, of the extent of drug company marketing in our lives; if I'm being manipulated I'd like to know it. The recent adoption by the AMA of guidelines for physicians in dealing with drug companies is also useful. It may also be useful to consider the issues locally. Two specific suggestions: 1) Hospital staffs might look into the extent of drug company involvement in their hospitals and set guidelines. 2) Programs might be set up with drug companies in which i) educational programs are partially supported by drug companies, ii) the drug companies are openly and warmly thanked for their support, iii) the choice of speakers is totally independent of the drug company, iv) reimbursement is through the hospital rather than the drug company. I recently discussed the latter proposal with a group of colleagues and I held that there was an inherent conflict of interest between direct support of a speaker by commercial interests and the academic nature of Grand Rounds. My colleagues' responses were not particularly supportive of my stand for "practical" reasons; they said that, in the past, generic contributions for educational programs have been sought from pharmaceutical industries without much success and that there would be significant costs (efforts and dollars) if Grand Rounds were to rely less on direct drug company help. Their response brought home to me the fact that, as Chren and Landefeld point out, it is tempting to avoid making ethical distinctions. Such distinctions, however, should be made in order to establish a healthier interaction between the drug industry and our profession.

Frederic G. Hoppin, Jr, MD
The Memorial Hospital of
Rhode Island

• • •

I found the article *Doctors, Drug Companies and Gifts* to be well written and very much to the point. As I looked around my office, I saw several pens, a few pads, a clock, a calendar and several medical books that were given to me by drug company representatives. I felt an immediate sense of discomfort and tried to reassure myself with the memory of a fairly recent article in *JAMA* which stated that gifts which had a value of under $100 did not influence prescribing practices of physicians. Nevertheless, it is not only the monetary value of these gifts which ultimately does add up to millions of dollars when all of the physicians in the country are considered, but it is the question of allocation of resources in general within the pharmaceutical company that concerns me. The article notes that five billion dollars are spent annually for marketing. A large number of my patients are elderly and do not have insurance that includes a prescription plan. Despite my efforts to reduce the number of their medications to an absolute minimum, many have multi-system disease and must be on several medications to control their symptoms or progression of their disease. Abdominal distress and ulcers are treated with medications that cost an average of $70-$80 per month. Many anti-hypertensive medications cost from $30-$60 per month. Many cardiac medications carry a monthly price tag in the range of $60-$70. I would like to see an accounting of the marketing budget which involves gifts to physicians for each of the companies whose representatives I see in the office. I would like to see a percentage of that budget devoted to reduction of price to the pharmacist and thus to the patient.

I propose that as patient advocates we all stop accepting gifts, however small, from the pharmaceutical companies. If we were all to do this collectively, I believe it would have quite an impact on the companies. Rhode Island is the ideal state to act as a leader in this movement; it is small enough for a concerted effort and there is currently active discussion of ethics at every level of government and private life. I would welcome hearing from any physicians on this subject.

Mary B. Preston, MD
Wakefield, RI

CARE plants the most wonderful seeds on earth.

Seeds of self-sufficiency that help starving people become healthy, productive people. And we do it village by village by village. Please help us turn cries for help into the laughter of hope.

There's more to Portable X-Ray Service than X-Rays.

Yes, our main business is to provide you with fast, efficient, diagnostic X-Ray services, but we have much more to offer . . . including a staff of people who really care.

- Diagnostic X-Ray Services
- EKG
- Holter-Monitoring*
- Ultrasound Services*
- Same day reporting
- 24 Hour Service
- Seven days a week

*by appointment only

We service the entire Greater Rhode Island area:

- Nursing and Convalescent Homes
- Shut-ins and Private Home Patients
- Post Surgical Patients

PORTABLE X-RAY SERVICE

OF RHODE ISLAND

Certified by the R.I. Department of Health. Reimbursement provided by Medicare, R.I. Blue Shield and Medical Assistance.

100 Highland Avenue Providence, R.I. 331-3996	120 Dudley Street Providence, R.I. 331-3996	154 Waterman Street Providence, R.I. 273-0450	38 Hamlet Avenue Woonsocket, R.I. 766-4224

You treated little Johnny for measles in kindergarten, chicken pox in 3rd grade, mono in high school.

But what can you do for his HIV today?

People with HIV are special patients with specific needs. That's why it helps to have experience with HIV when treating an infected patient–the kind of experience doctors find at Clinical Partners.

Clinical Partners is a group of healthcare professionals dedicated to helping patients live with HIV. We are alone in the complete array of services we provide to physicians, employers and insurers of those living with HIV. Our early intervention averts costly hospital stays, while increasing patient care and support.

Operating successfully in Boston, New York and Los Angeles, Clinical Partners is pleased to announce the first anniversary of our Providence office, under the expert guidance of Linda Durand NP, RNC and Deborah Matson CISW, MSW.

We want Rhode Island physicians to know Clinical Partners is here to help, and here to stay. As the patient's primary physician, you can benefit from our knowledge and experience, which is available to help you treat HIV infection and AIDS.

To find out how Clinical Partners can be your partner in treating HIV patients, call our Providence office today at 454-8880 or 1-800-285-8880.

Clinical Partners

Helping people make choices about HIV.

THE RHODE ISLAND MEDICAL JOURNAL

The Official Organ of the Rhode Island Medical Society
Issued Monthly under the direction of the Publication Committee

VOLUME I
NUMBER I

PROVIDENCE, R. I., JANUARY, 1917

PER YEAR $2.00
SINGLE COPY, 25 CENTS

THE RHODE ISLAND MEDICAL JOURNAL HERITAGE

Ninety Years Ago
(Providence Medical Journal)
(March, 1902)

The lead article is an editorial on suicide in adolescence, possibly prompted by the recent, tragic suicide of a college student in Providence. The editor states: "The philosophy of suicide is, and in its nature must always be, an unknown and impenetrable territory. We know well enough that the weak body, the body of little inhibitory power, is often the tenement of the gifted mind, and that a mind thus tenanted is easily disturbed as to the harmony of its mental and moral faculties. We have all known young people who intensify every impression into one of absolute pain or exquisite pleasure – who know no middle ground." He observes further: "In neurasthenia, a disease so woefully common in this country, enfeeblement of will and impulsiveness go hand in hand, thus permitting any idea to become fixed in the mind and be the origin of an obsession. For this and kindred reasons it has seemed to the writer that all large colleges would do well to have as an essential part of their polity a department through which young men might be watched, guided and aided from the point of view of personal, and especially mental, hygiene. All experienced medical men know something of the anguish of the soul that is often suffered by students during the stressful period of adolescence, and it will be readily understood what a real help it would be if they might go . . . and have gloomy apprehensions removed, fears set at naught, faulty perspectives corrected, and much else done for them that might make for their general welfare."

A second editorial proclaims the urgent need for a deliberate campaign of vaccination in Providence. The editorial notes with great concern that, "the small pox situation in New England continues to be alarming. The outbreak in Boston shows little signs of abatement, and from twenty-five to fifty cases are reported weekly." With regard to Rhode Island, "Conditions in Woonsocket are very unsatisfactory. New cases are found almost daily. Providence is an unvaccinated city. It is probable that there are considerably more than 100,000 people here who are unprotected by vaccination." The mortality of the disease at this time in New England is about thirteen to fourteen percent.

A third editorial advises that milk sellers in Rhode Island be licensed. "We firmly believe that under the proposed system, whose adoption we now urge, the milk supply of the city may be greatly improved, and the standard constantly maintained. It is hoped a large number of honest milk sellers will appreciate and welcome the measure, realizing that only rogues and tricksters in their ranks need be apprehensive of its action."

The principal scientific contribution in this issue is an article entitled, The Nature and Diagnosis of Glaucoma by FT Rogers, MD. Glaucoma, observes the author, constitutes about one percent of all diseases of the eye and its symptoms may so closely simulate other diseases that the diagnosis is missed, valuable time wasted, improper remedies applied, and vision frequently destroyed. Every practitioner should bear in mind three things. First, that there is such a condition as glaucoma which may resemble rheumatism, sick headache or toothache; second, that atropine is not a panacea for every ocular ill, and should never be used except with a full understanding of its action; and third, that the practitioner make himself acquainted with the tension of healthy eyes, that he may recognize the increased tension of glaucoma. The paper, by means of selected and illustrative case histories, emphasizes the three following issues: "1. The evil effect of a mydriatic. 2. The efficacy of prompt surgical treatment. 3. The danger of delay in making a diagnosis."

In the judgment of the author, "Glaucoma is a disease of advanced life. It seldom occurs in patients under forty-five or fifty years of age, more frequently occurring in women than in men and according to Fuchs, it is especially liable to attack women at a

premature menopause. It apparently runs in some families, and the Jewish race is certainly predisposed to the disease."

Fifty Years Ago
(March, 1942)

The lead contribution is the Providence Medical Association presidential address by Murray Danforth, MD.

HS Barrett, MD describes a case of leprosy. His patient is a 21-year-old Chinese male restaurant employee who entered the Chapin Hospital because of a chronic skin eruption involving his right thigh. He was born in Kwangtung Province, China where (it is said) leprosy is endemic. Physical examination revealed no sensory loss and routine laboratory tests were unremarkable. A skin biopsy was consistent with leprosy, but no organism was visualized. After initial therapy (with chaulmoogra oil), the patient was transferred to the National Leprosarium at Carville, Louisiana. The article concludes with a vivid description of attitudes and rituals during earlier centuries when a member of a community was identified as leprous.

F. Ronchese, MD writes on cancer of the skin. He notes that skin cancer may follow senile keratoses, cutaneous horns, leukoplakia, kraurosis vulvae, tertiary syphilitic lesions, dermatitis from X-ray or radium, arsenical keratoses, scars from burns or tuberculosis of the skin, chronic ulcers and fistulous sinuses, and ordinary moles. The article provides excellent photographs of skin cancers of the head, neck and extremities. The author concludes: "Cancer of the skin usually is easily recognized from the very beginning. Diagnosed as early as possible and properly treated, complete recovery is the rule. Proper treatment is accomplished by surgery, radium or X-rays, according to the type, extension and location. It is essential that treatment is performed in the shortest time and radically. The treatment of recurrences has always less chances of success."

The lead editorial announces the retirement of Dr Albert H. Miller who had been editor of the *Journal* for five years. Dr Miller is replaced by Dr Peter Pineo Chase. The editorial pages also note the deaths of three great leaders of clinical and research medicine: Kenneth D. Blackfan, MD (pediatrics), Soma Weiss, MD (internal medicine), and Lawrence J. Henderson, MD (clinical chemistry).

There are comprehensive instructions for all physicians to complete the Procurement and Assignment Service questionnaires, regardless of age, gender or physical condition. The present military needs are for physicians under 36 years of age and immediate commissions are available. Physicians over 36 should await receipt of the enrollment forms.

Twenty-Five Years Ago
(March, 1967)

The lead article is a summarization of a panel discussion, sponsored by the Rhode Island Medical Society, on highway traumata and their medical and surgical aspects. The symposium is chaired by FA Simeone, MD (shortly to transfer to Providence from Cleveland). Simeone observes that each year some 45 million people are injured in accidents involving a monetary loss of at least 15 billion dollars. In 1964, about 95,000 individuals died in accidents (vehicular, 40%; falls, 20%; fire, explosion, 8%; drowning 5%; other, 27%). A further observation: More hospital beds are used for the treatment of accident victims than for any other kind of illness. "Nearly 20 million hospital bed-days were utilized in 1964 for patients injured in accidents, twice as many as for heart disease."

Simeone notes that the incidence of automobile accidents is increasing in large cities, but that the mortality rate is decreasing. He speculates that this is ascribable to improved methods of accident treatment in the large medical centers. He concludes that an intimate understanding of shock and oligemia is necessary for the rational care of acutely injured persons. "The fate of the patient who has incurred a serious accident is often determined by what is done or not done at the scene of the accident and directly afterward."

AA Savastano, MD, discusses the management of orthopedic problems following automobile accidents. The central role of alcohol is emphasized. "It has been reasonably well established that 5 ounces of whiskey produces a 0.05 percent blood level. Taking into account that a 0.03 per cent blood level is enough to produce impaired vision, it is evident what 5 ounces of whiskey will do to one's driving." Savastano summarizes the various steps to be observed in treating an accident patient, including which tests should be undertaken. He states: "If the patient has multiple injuries involving several specialties, a "Take-Charge Surgeon" should be the overall responsible person in the case. The most serious injury should receive preferential attention."

Neurosurgical considerations following automobile accidents are discussed by J. Stoll, MD. The importance of skull X-rays is discussed. The dangers of intracranial hematomata and spinal cord trauma are noted as well as the difficulties in detecting them in an unconscious patient. While hypothemia has some uses, the author notes that this procedure may obscure subtle neurological deficits and mask signs of secondary infection. The value of steroids and dehydrating solution is discussed in instances of increased intracranial pressure.

Post-traumatic genitourinary tract injuries are reviewed by EK Landsteiner, MD. During a seven year interval, the Rhode Island Hospital observed 50 instances of traumatic injury to the kidney, about one in every 2,000 admissions. In cases of traumatic fracture of the bony pelvis, injuries to the urethra and bladder are common. "Treatment consists of cystotomy, closure of the rent in bladder and post-operative drainage. End results are usually excellent, but morbidity and mortality are directly related to delay in definitive operative treatment."

WW Francis, MD discusses ab-

dominal trauma caused by auto accidents. After noting that abdominal injuries are a frequent occurrence in vehicular trauma, he outlines the necessary steps to be undertaken following the patient's arrival in the accident room of a hospital. He discusses the need for immediate cutdown, nasogastric tube to decompress the stomach, indwelling catheter to empty the bladder and monitor urinary output, diagnostic abdominal taps, and various other measures to determine the extent and location of intra-abdominal injury.

CL Farrell, MD and M Goldberg, MD present two case reports of rupture of the rectus abdominis muscle. The first is a 51-year-old female who had experienced a coughing spell the night before hospital admission. Surgery revealed a rupture of the rectus abdominis and large amount of clotted blood. The patient recovered after surgical repair of the rupture. The second case is a 41-year-old laborer presenting with a right lower quadrant mass which was shown surgically to be a large hematoma associated with a rectus tear. No history of trauma.

P LaMarche, MD, AB Heisler, MD and NBS Kronemer, MD discuss disappearing mosaicism in the Trisomy 17-18 syndrome. They summarize their findings: "A female infant with many of the clinical characteristics of trisomy E 17-18 syndrome has been presented. Chromosome studies on peripheral blood performed at birth revealed a mosaicism of 90 % trisomic cells and 10% normal cells. At 10 months of age, repeat analysis of the chromosomes of peripheral blood leukocytes revealed only a normal female karyotype. Analyses done on direct bone marrow and skin chromosomes were also normal. From these data it is apparent that rations of mixocellular populations can be variable with time in mosaic individuals. It is postulated that in forme fruste syndromes having normal cytogenetic findings disappearing mosaicism is a possible mechanism."

The lead editorial advocates new freeway regulations. Specifically, "1) Denying to heavy trucks and buses use of center lanes on six-lane divided highways. 2) Forbidding hitchhikers on limited access highways." There are further editorial comments on the prevention of alcoholism, mortality from diseases associated with smoking and the dangers of indifferently treating clinically silent gallstones.

This issue of the *Journal* carries the eulogy by Rev JL Lennon for Congressman John E. Fogarty. The *Journal* notes that Representative Fogarty, who had contributed so much to health care legislation in Congress, was one of three honorary lay members of the Rhode Island Medical Society.

There must be a good reason why

UNITED SURGICAL CENTERS

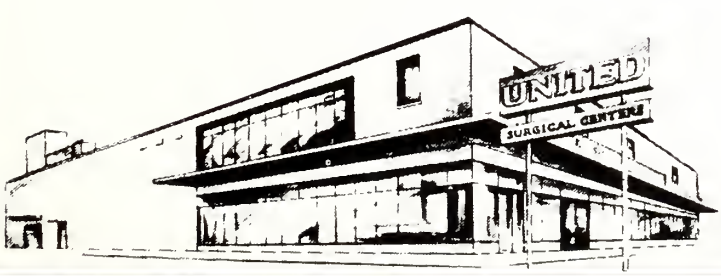
The Professionals in Home Health Care Equipment

we've become the trusted back-up resource for more Rhode Island doctors (and their patients) than anyone else.

We carry just about EVERYTHING for Home Health Care . . . which means, everything a patient or convalescent needs to implement the doctor's treatment directions. For Ostomy and Oxygen needs to Orthopedic Appliances, Wheelchairs, Walkers and Hospital Beds, we're here to serve your patients. Our staff is knowledgeable and dedicated to supplying exactly "what the doctor ordered". We've been doing it dependably for many years.

That's how we've earned the trust of so many doctors.

Medicare and Third Party Claims Accepted and Processed



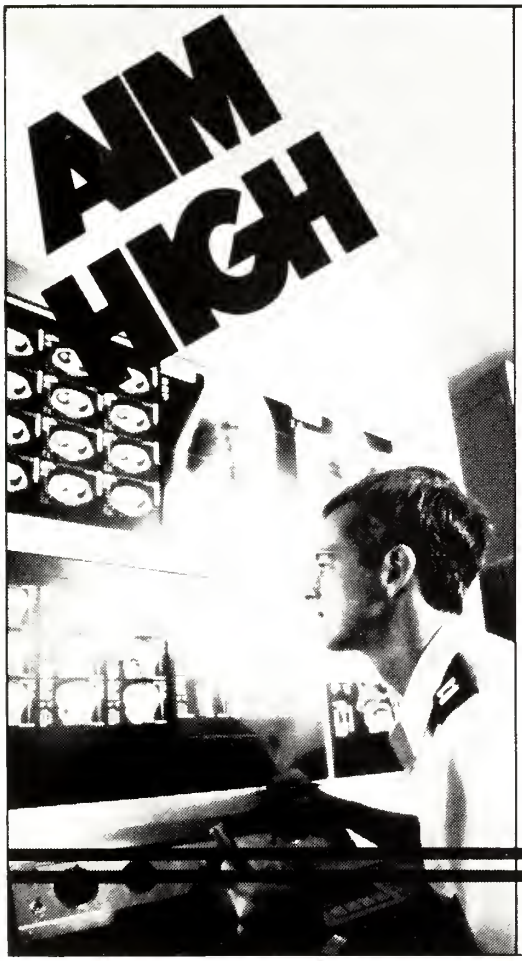
380 WARWICK AVE., WARWICK
781-2166

NURSE ANESTHESIA SERVICES OF NEW ENGLAND (NASNE)

serving Rhode Island hospitals with local CRNAs

- Specialists in TEMPORARY and PERMANENT placement of CRNAs
- NASNE provides local, experienced, highly-qualified CRNAs to Rhode Island hospitals
- NASNE's use of local CRNAs reduces your staffing costs by avoiding travel and other associated expenses
- Dependable and personalized service is provided by a staff that understands you and your scheduling needs

NASNE – the Rhode Island Specialists
Call us at 1-800-531-5319



SPECIALIZE IN AIR FORCE MEDICINE.

Become the dedicated physician you want to be while serving your country in today's Air Force. Discover the tremendous benefits of Air Force medicine. Talk to an Air Force medical program manager about the quality lifestyle , quality benefits and 30 days of vacation with pay per year that are part of a medical career with the Air Force. Find out how to qualify. Call

USAF Health Professions
Toll Free
1-800-423-USAF

AIR FORCE

Need Information about Businesses? Call the Business *INFOLINE!*

There are over 9 million businesses in the U.S. – and finding information about them can be virtually impossible, especially when you need it *fast*. But now there's a way . . . a revolutionary new service called *Business INFOLINE!* Need to know the address and phone number for "XYZ Company" somewhere in Florida, or the name and phone number of a "Cadillac Dealer" in Palm Beach? Even telephone company directory assistance can't help you in these situations . . . but we can!

For example . . .

"Your BMW breaks down on the interstate, and you need to know if there 's a dealer in the next town."

"An out-of-town company is trying to sell you vinyl siding for your house and you need more information about them – how long the company has been in business, and how many employees they have."

"You're planning a vacation in the Pacific Northwest, and you want to line up things for the kids to do. So you need to find the amusement parks and zoos in Oregon and Washington."

"A friend gave you a tip that "Apex Industries" would be a good investment, but you want to know more. What do they do? What are their approximate annual sales?"

The Business INFOLINE is indispensable for home or office? And the cost is *only* $3.00 for the first minute and $1.50 for each additional minute, conveniently billed to your phone number. The service is available Monday through Friday, 7:00 a.m. to 6:00 p.m., Central Time.

Dial 1-900-896-0000

Ask for Ext. #195

Money-back Guarantee if not satisfied.

A Service of American Business Information • 5711 So. 86th Circle • Omaha, NE 68127

Rural Health CARING for the country

National Rural Health Association
15th Annual Conference on Rural Health
May 6–9, 1992
Hyatt Regency Crystal City
Washington, DC

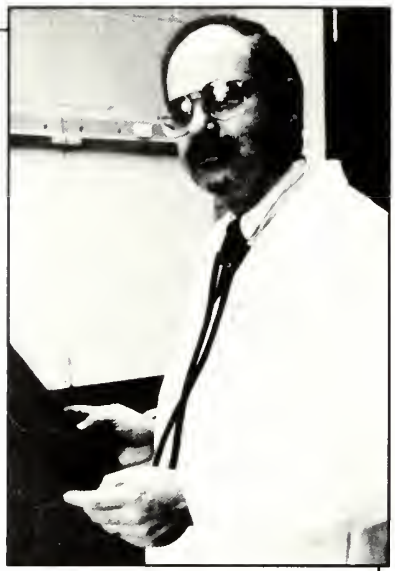
A critical health problem for your patient. A difficult problem for you to treat.

The Miriam Hospital Weight Management Service offers treatment programs addressing all levels of obesity. With over 10 years' experience in obesity treatment and research, our multidisciplinary team provides the resources needed for safe, medically monitored weight loss and for long-term success in maintaining weight loss.

For more information on our programs, or to refer a patient, call:
(401) 861-0870

Portions of our programs may be covered by health insurance.

The Miriam Hospital Weight Management Service
Division of Behavioral Medicine
An affiliate of the Brown University Medical School



Sure...

you're a good physician, but can you write?

Most physicians today need more than knowledge of medicine and good clinical ability to be successful. One of the tools you need is the ability to write well: to be able to put together a report of research that's worth publishing, to write a grant proposal that's fundable, to prepare a paper or exhibit for presentation that's well received.

We don't guarantee that you'll write a best seller or get a million-dollar grant, but we can guarantee that if you join us, you'll learn how to improve your writing, enhance the quality of your presentations, and keep up-to-date with developments in areas like desktop publishing.

We're an organization founded by physicians 50 years ago, and we're over 3000 strong. Among our members are people like you, for whom writing has become an increasingly important part of life. Find out more about us.

Send this coupon or call AMWA's national office at 301-493-0003.

Executive Director, AMWA
9650 Rockville Pike
Bethesda, MD 20814

AMERICAN MEDICAL WRITERS ASSOCIATION

Please send information about AMWA to:

Name _____

Address _____

_____

_____

Title (or specialty) _____

City _____ State ____ Zip ____

YOCON®
YOHIMBINE HCl

Description: Yohimbine is a 3a-15a-20B-17a-hydroxy Yohimbine-16a-carboxylic acid methyl ester. The alkaloid is found in Rubaceae and related trees. Also in Rauwolfia Serpentina (L) Benth. Yohimbine is an indolalkylamine alkaloid with chemical similarity to reserpine. It is a crystalline powder, odorless. Each compressed tablet contains (1/12 gr.) 5.4 mg of Yohimbine Hydrochloride.

Action: Yohimbine blocks presynaptic alpha-2 adrenergic receptors. Its action on peripheral blood vessels resembles that of reserpine, though it is weaker and of short duration. Yohimbine's peripheral autonomic nervous system effect is to increase parasympathetic (cholinergic) and decrease sympathetic (adrenergic) activity. It is to be noted that in male sexual performance, erection is linked to cholinergic activity and to alpha-2 adrenergic blockade which may theoretically result in increased penile inflow, decreased penile outflow or both.

Yohimbine exerts a stimulating action on the mood and may increase anxiety. Such actions have not been adequately studied or related to dosage although they appear to require high doses of the drug. Yohimbine has a mild anti-diuretic action, probably via stimulation of hypothalmic centers and release of posterior pituitary hormone.

Reportedly, Yohimbine exerts no significant influence on cardiac stimulation and other effects mediated by B-adrenergic receptors, its effect on blood pressure, if any, would be to lower it; however no adequate studies are at hand to quantitate this effect in terms of Yohimbine dosage.

Indications: Yocon® is indicated as a sympathicolytic and mydriatric. It may have activity as an aphrodisiac.

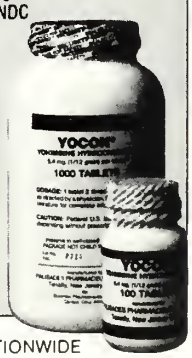
Contraindications: Renal diseases, and patient's sensitive to the drug. In view of the limited and inadequate information at hand, no precise tabulation can be offered of additional contraindications.

Warning: Generally, this drug is not proposed for use in females and certainly must not be used during pregnancy. Neither is this drug proposed for use in pediatric, geriatric or cardio-renal patients with gastric or duodenal ulcer history. Nor should it be used in conjunction with mood-modifying drugs such as antidepressants, or in psychiatric patients in general.

Adverse Reactions: Yohimbine readily penetrates the (CNS) and produces a complex pattern of responses in lower doses than required to produce peripheral a-adrenergic blockade. These include, anti-diuresis, a general picture of central excitation including elevation of blood pressure and heart rate, increased motor activity, irritability and tremor. Sweating, nausea and vomiting are common after parenteral administration of the drug.[1,2] Also dizziness, headache, skin flushing reported when used orally.[1,3]

Dosage and Administration: Experimental dosage reported in treatment of erectile impotence.[1,3,4] 1 tablet (5.4 mg) 3 times a day, to adult males taken orally. Occasional side effects reported with this dosage are nausea, dizziness or nervousness. In the event of side effects dosage to be reduced to ½ tablet 3 times a day, followed by gradual increases to 1 tablet 3 times a day. Reported therapy not more than 10 weeks.[3]

How Supplied: Oral tablets of Yocon® 1/12 gr. 5.4 mg in bottles of 100's NDC 53159-001-01 and 1000's NDC 53159-001-10.



References:

1. A. Morales et al., New England Journal of Medicine: 1221. November 12, 1981.
2. Goodman, Gilman — The Pharmacological basis of Therapeutics 6th ed., p. 176-188. McMillan December Rev. 1/85.
3. Weekly Urological Clinical letter, 27:2, July 4, 1983.
4. A. Morales et al., The Journal of Urology 128: 45-47, 1982.

Rev. 1/85

AVAILABLE AT PHARMACIES NATIONWIDE

PALISADES PHARMACEUTICALS, INC.
219 County Road
Tenafly, New Jersey 07670
(201) 569-8502
1-800-237-9083

INFORMATION FOR AUTHORS

Manuscripts: Manuscripts will be accepted for consideration with the understanding that they are original contributions, have never been published or submitted elsewhere, and are submitted only to the *Rhode Island Medical Journal.*

Specifications: Manuscripts must be original typed copy (not all capitals) on 8½ × 11 inch firm typewritten paper, double-spaced throughout (including title page, text, acknowledgments, and references) with margins of at least one inch and using but one side of each page. Tables, charts, and legends should be submitted separately from the text, and referred to by number (ie, Fig. 1) within the text. Subheadings must be inserted at reasonable intervals to break the typographic monotony of the text. Pages must be numbered consecutively. Italics and boldface print are never used except as subheadings.

Abbreviations: The *Journal* attempts to avoid the use of jargon and abbreviations. All abbreviations, especially of laboratory and diagnostic procedures, must be identified in the text.

Title Page: All manuscripts must include a title page which provides the following information: (1) a concise and informative title; (2) the name of the author or authors with their highest academic degree (ie, MD, PhD); (3) a concise biographical description for each author which includes specialty, practice location, academic appointment, and primary hospital affiliation; (4) mailing address and office telephone of principal author; (5) mailing address of author responsible for correspondence or reprint requests; (6) source of support if applicable.

Illustrations: Authors are urged to use the services of professional illustrators and photographers. Drawings and charts should always be done in black ink on white paper. Clear, black and white 5 × 7 glossy photographs should be submitted, and such illustrations numbered consecutively and their positions indicated in the text. Original magnifications should be noted. Illustrations defaced by handwriting or excessive handling will not be accepted. The figure number, indication of the top, and the name of the author must be attached to the back of each illustration. Legends for illustrations should be typewritten on a single list, with the numbers corresponding to those on photographs and drawings. Recognizable photographs of patients are to be appropriately masked and must carry with them written permission for publication. Special arrangements must be made with the editors for excessive numbers of illustrations. Color plates are not acceptable.

Identification of Patients: Names, initials should not be used. Use of numbers is a preferable form of identification.

Reprints: Because of cost considerations, reprints are not provided routinely to the author(s). Reprints may be ordered separately (100 copies minimum order) and printing costs will be charged to the author(s).

Responsibility: Manuscripts are subject to editorial revisions as deemed necessary by the editors and such modifications will be undertaken so as to bring them into conformity with *Journal* style, which is in compliance with the editorial standards of the AMA. However, neither the editors, nor the publishers, nor the Rhode Island Medical Society will accept responsibility for statements made or opinions expressed by any contributor in any article or feature published in the pages of the *Journal.*

Permission: When material is reproduced from other sources, full credit must be given both to the author and publisher of these sources. Where work is reported from a governmental service or institution, clearance by the appropriate authority must accompany the manuscript.

References: To conserve space and expense, references should be limited to those essential to the subject. The editor reserves the right to reduce the number when it is deemed necessary. The references must be double-spaced and numbered as they appear consecutively in the text, with their positions clearly indicated in the text. All references must be checked to assure complete accuracy. Each journal reference must include the full name of the author(s); complete title of paper; name of publication; volume number; issue number; first and last page of paper; and date (year, month, and day as indicated). Each book reference must include the full name of author(s), editor(s), or both, with initials; title of book; edition; publisher; location; year of publication, volume (if given); and page number. If the reference is to a chapter within a book, the author of the chapter, if different than the author of the book, and the title of the chapter (if any) must be provided.

Correspondence: All correspondence relating to publication should be addressed to: Managing Editor, *Rhode Island Medical Journal,* 106 Francis Street, Providence, RI 02903.

ONCE DAILY 180mg Calan SR Verapamil HCl 180 mg SUSTAINED-RELEASE CAPLETS

The recommended starting dose for Calan SR is 180 mg once daily. Dose titration will be required in some patients to achieve blood pressure control.

A lower initial starting dosage of 120 mg/day may be warranted in some patients (eg, the elderly, patients of small stature)

Constipation, which is easily managed in most patients, is the most commonly reported side effect of Calan SR

BRIEF SUMMARY

Contraindications: Severe LV dysfunction (see *Warnings*), hypotension (systolic pressure < 90 mm Hg) or cardiogenic shock, sick sinus syndrome (if no pacemaker is present), 2nd- or 3rd-degree AV block (if no pacemaker is present), atrial flutter/fibrillation with an accessory bypass tract (eg, WPW or LGL syndromes), hypersensitivity to verapamil.

Warnings: Verapamil should be avoided in patients with severe LV dysfunction (eg, ejection fraction < 30%) or moderate to severe symptoms of cardiac failure and in patients with any degree of ventricular dysfunction if they are receiving a beta-blocker. Control milder heart failure with optimum digitalization and/or diuretics before Calan SR is used. Verapamil may occasionally produce hypotension. Elevations of liver enzymes have been reported. Several cases have been demonstrated to be produced by verapamil. Periodic monitoring of liver function in patients on verapamil is prudent. Some patients with paroxysmal and/or chronic atrial flutter/fibrillation and an accessory AV pathway (eg, WPW or LGL syndromes) have developed an increased antegrade conduction across the accessory pathway, bypassing the AV node, producing a very rapid ventricular response or ventricular fibrillation after receiving I.V. verapamil (or digitalis). Because of this risk, oral verapamil is contraindicated in such patients. AV block may occur (2nd- and 3rd-degree, 0.8%). Development of marked 1st-degree block or progression to 2nd- or 3rd-degree block requires reduction in dosage or, rarely, discontinuation and institution of appropriate therapy. Sinus bradycardia, 2nd-degree AV block, sinus arrest, pulmonary edema and/or severe hypotension were seen in some critically ill patients with hypertrophic cardiomyopathy who were treated with verapamil.

Precautions: Verapamil should be given cautiously to patients with impaired hepatic function (in severe dysfunction use about 30% of the normal dose) or impaired renal function, and patients should be monitored for abnormal prolongation of the PR interval or other signs of overdosage. Verapamil may decrease neuromuscular transmission in patients with Duchenne's muscular dystrophy and may prolong recovery from the neuromuscular blocking agent vecuronium. It may be necessary to decrease verapamil dosage in patients with attenuated neuromuscular transmission. Combined therapy with beta-adrenergic blockers and verapamil may result in additive negative effects on heart rate, atrioventricular conduction and/or cardiac contractility; there have been reports of excessive bradycardia and AV block, including complete heart block. The risks of such combined therapy may outweigh the benefits. The combination should be used only with caution and close monitoring. Decreased metoprolol and propranolol clearance may occur when either drug is administered concomitantly with verapamil. A variable effect has been seen with combined use of atenolol. Chronic verapamil treatment can increase serum digoxin levels by 50% to 75% during the first week of therapy, which can result in digitalis toxicity. In patients with hepatic cirrhosis, verapamil may reduce total body clearance and extrarenal clearance of digitoxin. The digoxin dose should be reduced when verapamil is given, and the patient carefully monitored. Verapamil will usually have an additive effect in patients receiving blood-pressure-lowering agents. Disopyramide should not be given within 48 hours before or 24 hours after verapamil administration. Concomitant use of flecainide and verapamil may have additive effects on myocardial contractility, AV conduction, and repolarization. Combined verapamil and quinidine therapy in patients with hypertrophic cardiomyopathy should be avoided, since significant hypotension may result. Concomitant use of lithium and verapamil may result in a lowering of serum lithium levels or increased sensitivity to lithium. Patients receiving both drugs must be monitored carefully. Verapamil may increase carbamazepine concentrations during combined use. Rifampin may reduce verapamil bioavailability. Phenobarbital may increase verapamil clearance. Verapamil may increase serum levels of cyclosporin. Verapamil may inhibit the clearance and increase the plasma levels of theophylline. Concomitant use of inhalation anesthetics and calcium antagonists needs careful titration to avoid excessive cardiovascular depression. Verapamil may potentiate the activity of neuromuscular blocking agents (curare-like and depolarizing); dosage reduction may be required. There was no evidence of a carcinogenic potential of verapamil administered to rats for 2 years. A study in rats did not suggest a tumorigenic potential, and verapamil was not mutagenic in the Ames test. Pregnancy Category C. There are no adequate and well-controlled studies in pregnant women. This drug should be used during pregnancy, labor, and delivery only if clearly needed. Verapamil is excreted in breast milk, therefore, nursing should be discontinued during verapamil use.

Adverse Reactions: Constipation (7.3%), dizziness (3.3%), nausea (2.7%), hypotension (2.5%), headache (2.2%), edema (1.9%), CHF, pulmonary edema (1.8%), fatigue (1.7%), dyspnea (1.4%), bradycardia. HR < 50/min (1.4%), AV block total 1°,2°,3° (1.2%), 2° and 3° (0.8%), rash (1.2%), flushing (0.6%), elevated liver enzymes, reversible non-obstructive paralytic ileus. The following reactions, reported in 1.0% or less of patients, occurred under conditions where a causal relationship is uncertain: angina pectoris, atrioventricular dissociation, chest pain, claudication, myocardial infarction, palpitations, purpura (vasculitis), syncope, diarrhea, dry mouth, gastrointestinal distress, gingival hyperplasia, ecchymosis or bruising, cerebrovascular accident, confusion, equilibrium disorders, insomnia, muscle cramps, paresthesia, psychotic symptoms, shakiness, somnolence, arthralgia and rash, exanthema, hair loss, hyperkeratosis, macules, sweating, urticaria, Stevens-Johnson syndrome, erythema multiforme, blurred vision, gynecomastia, galactorrhea/hyperprolactinemia, increased urination, spotty menstruation, impotence.

4/11/91 • P91CA6277V

Address medical inquiries to
G.D. Searle & Co.
Medical & Scientific
Information Department
4901 Searle Parkway
Skokie, IL 60077

SEARLE *G.D. Searle & Co.*
Box 5110, Chicago, IL 60680

A91CA6148T

ONCE DAILY 180mg Calan SR Verapamil HCl 180 mg SUSTAINED-RELEASE CAPLETS
A MILD START IN MILD HYPERTENSION
When diet and exercise alone are not enough...
© 1991, G.D. Searle & Co.

RHODE ISLAND MEDICINE

April 1992

Volume 75, Number 4

Schistosomiasis

FRANCIS A COUNTWAY LIB OF MED
EXCHANGE OFFICE
10 SHATTUCK STREET
BOSTON MA 02115

Before you join an HMO...
Make sure you give ours a thorough examination.

First, check out our tagline.
The Ultimate Health Maintenance Organization.

Very simply, we feel we're the best HMO in Rhode Island. For the thousands of people enrolled in our plan. And for you.

That's why we'd like you to join our network of Participating Physicians. And invite you to examine HMO Rhode Island closely. *Very* closely.

You'll find only we offer you the following:

- ✔ Competitive fee schedules. We offer higher office visit allowances than other major plans. And payment terms for our Primary Care Physicians are available in either capitated or fee-for-service arrangements.
- ✔ Responsive provider relations. Including easy access to both our Medical Director and Provider Relations Staff.
- ✔ Minimal paperwork. No administrative hassles.
- ✔ Service that will more than satisfy you. When we surveyed HMO Rhode Island physicians, an overwhelming number responded as being *very* satisfied with the service they receive from us.
- ✔ An open-door policy when it comes to decisions that affect the future of HMO Rhode Island.
- ✔ Plus, an emphasis on preventive care that puts the focus on you. As an HMO Rhode Island Primary Care Physician, you provide the guidance for your patient in all healthcare decisions.

Look interesting? Let **Physician Recruitment Manager, Carin Cookman** fill you in on the details. When it comes to all HMO Rhode Island has to offer, *seeing is believing.*

HMO
RHODE ISLAND

Call today: 274-6674 or 1-800-528-4141.

RHODE ISLAND MEDICINE

EDITORIAL STAFF

Stanley M. Aronson, MD
Editor-in-Chief

Kimberly A. Poulton
Managing Editor

Hugo Taussig, MD
Book Review Editor

Seebert J. Goldowsky, MD
Editor-in-Chief Emeritus

EDITORIAL BOARD

*Edward R. Feller, MD
Chairman

*Joseph Amaral, MD

*Stanley M. Aronson, MD

Edward M. Belser, PhD, JD

Paul Calabresi, MD

*Richard A. Carleton, MD

Margaret Cololan, MSJ

*James P. Crowley, MD

*Peter A. Hollmann, MD

*Margaret A. Neill, MD

*Frank J. Schaberg, Jr., MD

*Fred J. Schiffman, MD

William J. Waters, Jr., PhD

*Member of Publications Committee

OFFICERS

Kathleen C. Hittner, MD
President

Robert E. Baute, MD
President-Elect

A. Robert Buonanno, MD
Secretary

Frances P. Conklin, MD
Treasurer

Richard Wong, MD
Immediate Past President

DISTRICT AND COUNTY PRESIDENTS

Fred Vohr, MD
Bristol County Medical Society

William F. Coscina, MD
Kent County Medical Society

Orest Zaklynsky, MD
Newport County Medical Society

David P. Carter, MD
Pawtucket Medical Association

James P. Crowley, MD
Providence Medical Association

Joseph R. Dotolo, MD
Washington County Medical Society

Patrick R. Levesque, MD
Woonsocket District Medical Society

Volume 75, Number 4 April 1992

TABLE OF CONTENTS

COMMENTARIES

171 Schistosomiasis
G. Richard Olds, MD
Paul M. Knopf, PhD

Alfred W. Senft, MD

The Language of Epidemiology (X.) Relative and Attributable Risk

CONTRIBUTIONS – SCHISTOSOMIASIS
Guest Editors: G. Richard Olds, MD & Paul M. Knopf, PhD

176 **A Brief History of Schistosomiasis**
Kenneth S. Warren, MD

179 **Clinical Schistosomiasis**
Peter M. Wiest, MD
G. Richard Olds, PhD

187 **Nutritional Status and Child Growth in Schistosomiasis**
Stephen T. McGarvey, PhD, MPH

191 **Cytokines, Hepatic Fibrosis and Schistosomiasis**
Thomas F. Kresina, PhD
Quing He, MD, PhD
Mark A. Zern, MD

200 **Modern Approaches to Development of Vaccines Against Schistosomes**
Paul M. Knopf, PhD
Parmjeet K. Suri, PhD

208 **The Hemoglobinase of *Schistosoma mansoni***
James H. McKerrow, MD, PhD

212 **Chemotherapy of Schistosomiasis**
Mahmoud H. el Kouni, BSc (Hon), MSc, MA, PhD

217 **A Look Ahead in Research and Control of Schistosomiasis**
Joseph A. Cook, MD, MPH
Jeffrey W. Mecaskey, MSc

COLUMNS

222 HEALTH BY NUMBERS
Rhode Island's Lead in School and Preschool Drinking Water Program

225 THE RHODE ISLAND MEDICAL JOURNAL HERITAGE

Cover: Schematic drawing of a Schistosome cercaria. Copyright cover illustration and all illustrations in content are by Mary Elizabeth Gordon.

Rhode Island Medicine is owned and published monthly by the Rhode Island Medical Society, 106 Francis Street, Providence, Rhode Island 02903, Ph: 401-331-3207. Single copies $2.00 — Subscriptions $20.00 per year (members of the Rhode Island Medical Society — $5.00 annually). Published articles represent opinions of the authors and do not necessarily reflect the official policy of the Rhode Island Medical Society unless clearly specified. Advertisements do not imply sponsorship or endorsement by the Rhode Island Medical Society. Second class postage paid at Providence, Rhode Island. ISSN 1061-222X. POSTMASTER: Send address changes to RHODE ISLAND MEDICINE, 106 Francis Street, Providence, RI 02903. National Advertising Bureau: State Medical Journal Advertising Bureau, Inc., 711 South Blvd., Oak Park, Illinois 60302. Phone 708-383-8800

You treated little Johnny for measles in kindergarten, chicken pox in 3rd grade, mono in high school.

But what can you do for his HIV today?

People with HIV are special patients with specific needs. That's why it helps to have experience with HIV when treating an infected patient–the kind of experience doctors find at Clinical Partners.

Clinical Partners is a group of healthcare professionals dedicated to helping patients live with HIV. We are alone in the complete array of services we provide to physicians, employers and insurers of those living with HIV. Our early intervention averts costly hospital stays, while increasing patient care and support.

Operating successfully in Boston, New York and Los Angeles, Clinical Partners is pleased to announce the first anniversary of our Providence office, under the expert guidance of Linda Durand NP, RNC and Deborah Matson CISW, MSW.

We want Rhode Island physicians to know Clinical Partners is here to help, and here to stay. As the patient's primary physician, you can benefit from our knowledge and experience, which is available to help you treat HIV infection and AIDS.

To find out how Clinical Partners can be your partner in treating HIV patients, call our Providence office today at 454-8880 or 1-800-285-8880.

ClinicalPartners

Helping people make choices about HIV.

COMMENTARIES

THE ARNOLD A. COUNTWAY
LIBRARY OF MEDICINE
BOSTON, MA
APR 15 1992

Schistosomiasis

In this special issue of *Rhode Island Medicine* we have attempted to present a variety of topics related to the parasitic disease Schistosomiasis. This issue is dedicated to the memory of our friend and colleague Dr Alfred Senft who devoted most of his professional life in research on this helminth. During many of the early years at Brown Dr Senft was alone in this pursuit. He was later joined by one of us (PK) and Dr Mahmoud el Kouni. Five years ago the other of us (GRO) came to Brown and brought with him Drs Tom Kresina, Peter Wiest and Tim Flanigan from Case Western Reserve University. More recently the Brown faculty was joined by Dr Mark Zern and Dr Stephen McGarvey both of whom work in this area. In total the Brown Schistosomiasis "team" currently includes seven Brown faculty and is supported by several individual NIH grants, one NIH program project, several WHO grants and by a variety of grants from private foundations. This work also involves extensive collaborative programs with partnered institutions in the Philippines, China and Egypt as well as research institutions in Australia and England. Research in Schistosomiasis at Brown, originally begun by Dr Senft, now is considered to be among the largest groups dedicated to the conquest of this parasite in the world.

We have attempted to organize this monograph from an initial chapter on clinical Schistosomiasis to a variety of monographs which summarize several of the broad areas of scientific investigation directed at this worm. These include an invited article by Dr James McKerrow of Stanford University which includes the work on the schistosome hemoglobinase enzyme which is most associated with Dr Senft's career. An introductory article on the history of this parasitic infection was written by Dr Ken Warren, a long time friend and colleague of Dr Senft's while a concluding article on the future of the field was contributed by Dr Joseph, another old friend and colleague of Dr Senft.

We hope that the readers find this issue of interest. Although not a major health problem to the average Rhode Islander, Schistosomiasis infects over 300 million individuals worldwide and is perhaps the leading cause of hepatic fibrosis on this planet. The schistosome story also represents one of the truly ingenious adaptations to life within the human host. Already research into this infection has told us much about immune evasion, resistance to infection and immunopathology in general. Finally the recent advances in science and technology as well as the recent development of single dose curative chemotherapy against this infection may make it possible to control this disease within our lifetime. A claim which perhaps cannot be made for many of the diseases which predominantly affect our local citizens.

G. Richard Olds, MD
Paul M. Knopf, PhD

Alfred W. Senft, MD

In 1968 at a time when tropical diseases were thought to be confined exclusively to the tropics, Brown University recruited Alfred Senft to teach clinical parasitology to its medical science students. Brown was still four years from its decision to establish an MD-granting school of medicine, and Al Senft became one of a very small cadre of faculty who assembled the original curriculum of the school. In the subsequent two decades, Senft continued a distinguished, world-famous career in schistosomiasis research, established an outstanding teaching effort in the pathophysiology and pharmacology of parasitic disease, and provided consultative service on tropical disease to virtually every hospital in Rhode Island. A few years ago, Senft retired to his beautiful home in Woods Hole to continue his research on schistosomal disease. Tragically, he then developed a rapidly expanding glioma and despite all efforts, died in early 1991. The editors of *Rhode Island Medicine*, in acknowledgment of his immense contribution to this community, and to the field of schistosomiasis research, respectfully dedicate this issue to Dr Alfred W. Senft.

Senft was born in the small town of Windsor, Colorado in 1924, the son of missionaries. His preprofessional education was undertaken both overseas as well as in the states. His MD degree was from Harvard and his various degrees in public health were granted by the London School of Tropical Medicine & Hygiene and the Harvard School of Public Health. His years of private general practice embraced both the challenges of New Guinea in the far east and the relative tranquility of New England's Cape Cod. During all of his years of practice he managed somehow to continue his

pursuit of parasitological research with funding from virtually every major health foundation. Senft was named a consultant to the World Health Organization and the National Institutes of Health. In almost four decades of fruitful activity he was honored with visiting professorships to numerous Asian, African and European universities.

Professor Senft's published research covered a wide range of inquiries from electrocardiographic observations on finback whales to the molecular biology of the schistosome worms. He contributed materially to the world's literature on parasitic disease and was instrumental in devising *in vitro* technics for the therapeutic testing of new antihelminthic drugs. He also discovered some of the proteolytic enzymes elaborated by the schistosome worms, providing us with greater insights into the mechanisms by which schistosomes sustain themselves in the human host. This ultimately formed the basis for certain diagnostic laboratory tests designed by Senft.

When Senft began his work in parasitology almost four decades ago, a tropical disease posed little visible threat to the health of the American population. Then came three social happenings: many of our young people in the Armed Forces traveled to places such as Viet Nam; many civilians of Caribbean and southeast Asian nations migrated to the United States; and increasing numbers of Americans voluntarily vacationed or worked in unconventional tropical locales. The result of all of these travels – voluntary and involuntary – has been a measurable increase in the incidence of parasitic disease in the United States. There are now an estimated 400,000 cases of schistosomiasis in the United States (more than twice the number of cases of multiple sclerosis).

What kind of a man was Senft? A deeply religious person with the zeal, commitment and tenacity of a missionary; the skepticism of a molecular biologist; and the tolerant humanity of a rural general practitioner. In truth, he was all of these, and much more. He possessed a child-like curiosity and a profound respect for all living things.

Those of us who knew him well deeply miss his renaissance strengths, his talent, his creative mind and his compassionate spirit.

Stanley M. Aronson, MD

The Language of Epidemiology (X.) Relative and Attributable Risk

Risk in epidemiological terms, is a numeric measure of the probability that a particular happening, usually an unpleasant hazard, will take place within a stated time interval. In this sense all risks are calculated – if not by the risk taker then by the epidemiologist. Inclusion of the time element is essential in the definition of risk; without it, the utility of risk as a predictive instrument becomes meaningless. What, for example, is the risk of mortality from any cause within 90 days? This question has meaning. On the other hand, what is the risk of mortality at some time in the future? Obviously, given our finite life spans, the answer will always be 1.0 (ie, 100%) regardless of the presence or absence of any risk factors.

Risk expressed quantitatively can always be compared with other risks; this new measurement is called Relative Risk (RR) and represents the simple ratio of two contrasted risks, thus serving to indicate the etiological weights of the examined risk factors. For example, let us say that the incidence rate of lung cancer in the nonsmoking (unexposed) adult male population is 18 per 100,000 per year and in male adult cigarette smokers (exposed), 165 per 100,000 per year. The RR (165/18 = 9.2) tells us that adding the variable of smoking to a fraction of an otherwise indistinguishable population of adult males increases the likelihood of lung cancer about nine-fold. Smoking of course is not an absolute yes-or-no risk; there are varying magnitudes of smoking. It would strengthen the contention that smoking causes lung cancer, then, if a dose-relationship between smoking and subsequent lung cancer could be established. When the smoking population is categorized by the average cigarette consumption per day, the RR for those smoking 1 to 9 cigarettes per day is 4.6, for 10 to 19 cigarettes, 8.6 and for those smoking more than 40 cigarettes per day, 18.8. The RR is thus shown to rise as intimacy with the risk factor of smoking increases. The general formula for Relative Risk is:

$$RR = \frac{\text{Risk (in exposed population)}}{\text{Risk (in unexposed population)}}$$

In groping for other etiologic forces for lung cancer, epidemiologists will inevitably find RRs equal to 1, signifying that the analyzed factor does not modify the basic risk. For example in a well-regulated study the risk of lung cancer in those watching Monday night football is the same as those who refrain from watching. (This of course, does not mean that TV watchers are immune to other ills such as couch decubitus ulcers or obesity.)

The full implications of relative risk can be appreciated only when it is weighted along with the compared incidence rates. In a 1981 study the Royal College of General Practitioners reported that the risk of cardiovascular mortality was increased about fourfold in women using oral contraceptive agents. However, the actual rise in mortality was from 6 to 26 per 100,000 per year. The RR was indeed 4.3 but the augmented risk was quite small, rising from 0.006% to 0.026%.

There is yet another means of characterizing the causative burden of determined risk factors. For example consider the problem of leg fracture in male undergraduate college students. Among those males who regularly engage in varsity sports (the exposed population), the rate is 140 per 100,000 per year (ie, 0.14%). Among the sedentary non-athletes (the unexposed population), the rate is 49 per 100,000 per year and the RR = 2.9. We may now wish to know what fraction of all collegiate fractures, expressed as a percent, may be ascribed to athletic activity, the Attributable Risk (AR).

The formula for this measure of excess frequency of a disease in a studied community is:

$$AR = \frac{\text{Risk (exposed)} \times 100}{\text{Risk (exposed)} + \text{Risk (unexposed)}}$$

$$AR = \frac{140 \times 100}{140 + 49} = 74.1\%$$

Given these data, we may now say that 74.1% of leg fractures in male undergraduate college students may be attributed to the risk factor of organized athletic activity. This assumes, first, that the data are accurately gathered and derived from random samples of the two collegiate populations (ie, athletes and non-athletes), and second, that the two populations are otherwise similar. The second assumption, particularly, must be verified before either the RR or AR can be believed. For example, coronary artery disease is significantly more common in naval officers than in enlisted naval personnel. It would be naive to attribute this selectively increased morbidity to the burdens of leadership since the two populations are not otherwise the same. Amongst many other differences, naval officers with command responsibilities are, on average, over 18 years older than enlisted sailors and age *per se* is a known risk factor for cardiovascular disease.

Herodotus said that great deeds are wrought at great risks. But we have no documented record that he ever smoked or rode his chariot without a seatbelt.

Stanley M. Aronson, MD

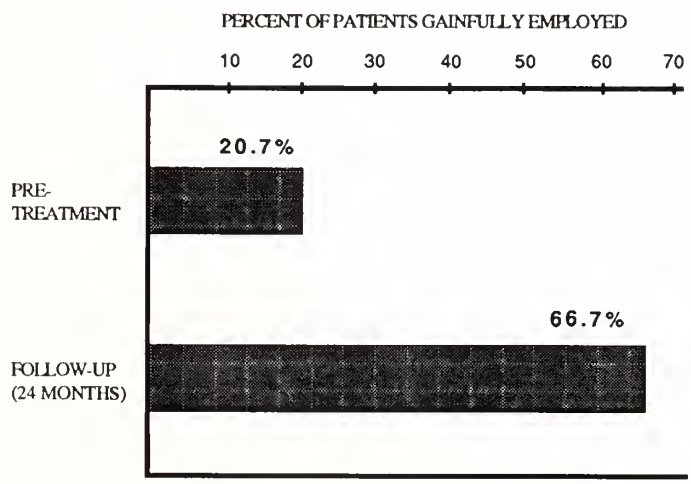
May, 1992
Contents

RHODE ISLAND
MEDICINE

Panic Disorder

Guest Editor:
Martin Keller, MD

"CHRONIC PAIN DOESN'T HAVE TO MEAN CHRONIC DISABILITY FOR YOUR PATIENTS..."



The Chronic Pain Treatment Program
(401) 751-9150

Institute for Behavioral Medicine
120 Wayland Avenue
Providence, Rhode Island 02906-4318

Are your investments as successful as you are?

*I*f your hard work and success have allowed you to build a portfolio of $250,000 or more, we'd like to work with you.

account administrator who will act as your personal financial advisor and you'll be backed by a team of investment

[*Professionally Managed Investments*]

Because at Citizens Bank, our Trust and Investment Management team can provide you with the exceptional service, experience, and performance that will help you get the most from your investments. You'll have an managers with a history of proven investment success.

To put us to work for you call Malcolm Starr at 456-7445. Because there's never been a better time for Citizens.

Trust and Investment Management Services

CITIZENS BANK

Citizens Trust Company/Citizens Savings Bank

RIMS
Insurance Brokerage Corporation

Insurance Professionals serving Health Care Professionals.

We do it better!

- Because our purpose is to serve RI doctors and allied health care professionals.
- Because our staff has 15 years of solid experience in medical liability underwriting.
- Because our board of directors is composed predominately of doctors with the same problems, stresses and concerns as you.
- Because we support political action in matters of health care benefiting all Rhode Islanders.
- Because our bottom line is superior service.

Phone 272-1050 — ask for Shirley and
Learn How We Can Do It Better For You!

RIMS Insurance Brokerage Corporation
The Experts in Medical Liability Insurance

Now offering up to 2M/4M limits for select insureds.

Also offering workers' compensation.

RIMS Insurance Brokerage Corporation
One Hayes Street, Providence, Rhode Island 02908
Phone (401) 272-1050 FAX (401) 272-1051

A Brief History of Schistosomiasis

Kenneth S. Warren, MD

Schistosomiasis is the most ancient of proven infections, found in mummies several millennia old in both Egypt and China.

Schistosomiasis is the most important worm infection of humans, not because of its relatively low prevalence, only 200 million as compared with ascaris, trichuris and hookworm which each infect about a billion, but because of its pathogenicity. Schistosomiasis is the most ancient of proven infections, found in mummies several millennia old in both Egypt and China. In the former, with its association with Nile, it has always been considered the major disease; in the latter, Chairman Mao wrote of schistosomiasis as the "plague spirit" and instituted a massive campaign to eradicate it from his people. *Schistosoma mansoni* which occurs in Africa, South America and the Caribbean, and *S. japonicum*, found in China and Southeast Asia, cause severe, chronic liver disease. *S. haematobium* of Africa and the Middle East is associated with urinary tract disease and vesical cancer.

Parasitology

In 1852, during an autopsy at Kasr El Aini Hospital in Cairo, Theodor Bilharz, a young German physician, observed, "After my attention had been drawn to the liver I soon found a white long helminth in the blood of the portal vein which I immediately recognized as something new." In a later paper he stated, "This has not developed into a fairy tale as I had assumed, but something more miraculous – a trematode with separate sexes." Sixty years later the life cycle of the parasite was discovered in Japan by Miyairi and Suzuki. Their response on determining that the infection alternated generations between snail intermediate hosts and mammalian definitive hosts was, "This is it, this is it, we shouted, and our joy knew no bounds."

Disease

Clinical manifestations of urinary schistosomiasis such as hematuria were observed in ancient Egypt and were reported from South Africa in 1864. Bilharz actually described the underlying pathology of the bladder in 1856. In contrast, the association of chronic liver disease, characterized by hepatomegaly and splenomegaly, with *S. mansoni*, and by inference, *S. japonicum*, was not apparent until Symmers' description of clay pipe stem cirrhosis in Egypt in 1904 and Say's report on splenomegaly in 1924.

Pathogenesis

Based largely on human clinical and pathological evidence a variety of etiological theories arose emphasizing either schistosome eggs, male worm infections, toxins, dead worms, or malnutrition. It was not until the late 1950s, when a mouse model of *S. mansoni* infection with hepatosplenomegaly, portal hypertension and esophageal varices was developed, that the parasitic factor was determined to be the schistosome eggs trapped in the presinusoidal venules of the liver. Subsequently, the crucial role of the host granulomatous response to the eggs was demonstrated and shown to be an inflammatory reaction of the cell-mediated immune type. Thus, schistosomiasis was revealed to be essentially an immunological disease.

Epidemiology

Helminths, including the schistosomes, are unique among all infectious agents in that they do not multiply within the human definitive host. With respect to schistosomiasis, it was not realized until the early 1970s that chronic disease often takes a decade to develop and is associated with heavy worm burdens. As environmental exposure to infection is sporadic, it takes years to acquire large numbers of

Kenneth S. Warren, MD, is Director for Science, Maxwell Macmillan Group, New York, New York.

worms, and with over-dispersion, this occurs in only 5-10% of exposed populations. Although immunity does not appear to play a determining role in the natural host-parasite balance, its mechanisms have been studied extensively in experimental animals and a large number of protective antigens have been reported as possible vaccines.

Diagnosis

The surest means of diagnosing schistosomiasis is to find eggs in the urine or feces. For many years serological and skin tests were a major area for research. The recent development, however, of simple and rapid method for quantification of eggs in the excreta have now rendered these non-quantitative immunological tests obsolete, particularly inasmuch as the worm burden is a major determinant of disease.

Treatment

In the Anglo-Egyptian Sudan in 1916 Christopherson discovered an effective schistosomicide called tartar emetic. This highly toxic antimony compound, administered in multiple, large intravenous doses, was the mainstay of the treatment of schistosomiasis for 60 years. During most of this period, the relation of disease to heavy worm burdens was not apparent. Thus, not only did the great majority of patients treated with this potentially lethal compound not require it, but it was also used in massive control and eradication campaigns in Egypt and China. It has been stated that more people were killed with tartar emetic than ever died from schistosomiasis alone. Fortunately, over the last twenty years many new and better antischistosomal drugs have been developed, culminating in the present drug of choice, praziquantel, a non-toxic, single-dose broad spectrum compound for all trematodes and cestodes.

Prevention

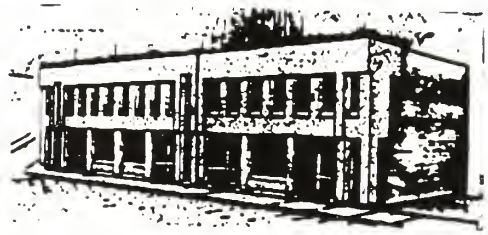
Praziquantel has revolutionized the control of schistosomiasis. Less than a decade ago control systems included not only relatively toxic drugs, but molluscicides, water supplies and sanitation. This multi-faceted strategy was both highly complex and exceedingly expensive. Now, based on the concept of control of disease rather than infection, ie, keeping worm burdens below the threshold of disease induction, the use of praziquantel alone targeted to heavily infected population groups and administered at intervals of 3 to 5 years, is both highly effective and very low in cost. Furthermore, it can be administered with other new broad spectrum antihelminthics to prevent virtually all disease associated with human helminth infection.

Schistosomiasis was revealed to be essentially an immunological disease.

During the last 35 years, when all of these remarkable developments in the understanding, diagnosis, treatment and control of schistosomiasis were occurring, I was working shoulder to shoulder with my admired friend and colleague, Dr Alfred Senft. As is usual in our Darwinian world, the development of new ideas and approaches were embroiled in controversy and turmoil. Nevertheless, the fittest ideas have survived and it is comforting to know that Al could see the goal in sight since he was deeply involved in the newly developing global campaigns to control schistosomiasis and all of the other helminth infections which have, since time immemorial, killed and maimed the people of this world.

Address correspondence to:
Kenneth S. Warren, MD
Director for Science
Maxwell Macmillan Group
New York, NY 10022

CONDOMINIUMS
FOR SALE OR LEASE



845 NORTH MAIN STREET
PROVIDENCE, RI

• Professional Office and Retail Space
• Convenient Access to I-95
• Minutes from downtown Providence, the Hospitals and Universities
• Ample On-Site Parking

CONTACT: CINDY MORSE, CCIM
PETER M. SCOTTI & ASSOCIATES
60 Ship Street, Providence, RI 02903
CCIM
401-421-8888

RHODE ISLAND MEDICAL BUREAU, INC.

"SMILES BEHIND THE VOICES"

The only answering service in Rhode Island, **exclusively** for the medical profession.

The **only** answering service that provides **live operator-patient communication**.

The only **staff specialized** in taking consults, lab reports, hospital messages, patient stress calls, etc.

The only answering service with a monthly **flat fee** for unlimited calls or paging.

GIUSI R. DE LUCA, MANAGER

421-1236

You don't have to do anything, we will set up your line(s) for you.

Clinical Schistosomiasis

Peter M. Wiest, MD
G. Richard Olds, MD

Schistosomiasis is a parasitic worm disease that infects over 200 million individuals, almost all of whom live in underdeveloped countries throughout the world.

Schistosomiasis is a disease that generally evokes vague recollections of first year medical school lectures or a winner in a medical school Trivial Pursuit game. In fact, schistosomiasis is one of the major health problems in the world, but because it attracts little attention from the industrially developed countries, it is considered one of the great neglected diseases of mankind. Schistosomiasis is a parasitic worm disease that infects over 200 million individuals, almost all of whom live in underdeveloped countries throughout the world. Even within these countries, schistosomiasis generally affects those in the lowest social and economic strata. Due to expansion of agricultural programs in endemic countries today, the prevalence of schistosomiasis is on the increase.

Peter M. Wiest, MD, is with the Division of Geographic Medicine, International Health Institute, Brown University and Department of Medicine, The Miriam Hospital, Providence, Rhode Island.

G. Richard Olds, MD, is with the Division of Geographic Medicine, International Health Institute, Brown University and Department of Medicine, The Miriam Hospital, Providence, Rhode Island.

In the United States, human infection with schistosomiasis has been estimated to exceed 400,000 individuals. These cases are mainly immigrants from endemic areas such as Africa, Puerto Rico, Brazil, the Philippines, and Southeast Asia. In addition, travelers and workers in endemic countries, such as Peace Corps volunteers, also become infected.

Physicians in the United States must become aware of schistosomiasis since, in recent years, travel to underdeveloped countries for business and pleasure has significantly increased and the number of individuals immigrating from underdeveloped countries is similarly increasing. These individuals may become ill, and upon presentation to a physician in the United States, their problem may be misdiagnosed. A typical example of this is presented in the recent case referred to The Miriam Hospital summarized in Figure 1.

For physicians in Rhode Island, several groups of immigrants have settled in the state and thus the diagnosis of schistosomiasis must be considered. For example, *Schistosoma mekongi* may infect Southeast Asians from such countries as Laos or Cambodia. Rhode Island has one of the largest Southeast Asian populations in the United States. In addition, Rhode Island has a large West African population from Liberia, Cote d'Ivoire, Ghana and Nigeria as in the example used before. These individuals may be infected with *Schistosoma mansoni* or *Schistosoma haematobium*. Immigrants from Brazil or Puerto Rico may harbor *Schistosoma mansoni*.

The diagnosis of schistosomiasis may not be straightforward. Clinical manifestations of schistosomiasis may be confused with other more common diseases seen in the United States. For example, the young patient from West Africa which presented with hematuria was confused with bladder carcinoma. In retrospect, *S. haematobium* is a leading cause of hematuria in that part of the world and could have been easily diagnosed non-invasively. On several occasions, patients have been referred with *S. mekongi* infection where the diagnosis was made on open liver biopsy as part of a portal caval shunting procedure. This diagnosis could have been made far less invasively from either a stool for O&P or even from the characteristic fibrotic pattern observed on abdominal CT.

ABBREVIATIONS USED:
CT: computerized tomography
ETOH: ethanol
O&P: ova and parasites

The objective of the following article is to provide an overview of schistosomiasis for physicians in Rhode Island. We hope this will allow Rhode Island physicians to consider this diagnosis when appropriate and to treat successfully. Furthermore, pitfalls in this diagnosis will be discussed.

Adult schistosomes exist within man as separate male and female worms.

Schistosomiasis is caused by a blood fluke or flatworm (trematode) that lives within the vasculature of the host. These helminths are up to 1-2 cm in length. Adult schistosomes exist within man as separate male and female worms. Sexual multiplication of the parasite, however, does not occur within humans in contrast to rapidly multiplying bacteria or viruses. Thus, the total number of adult worms in an individual is entirely dependent on the number of organisms that enter the individual at the time of infection.

Man species of schistosomes infect man. The species of primary importance are shown in Table 1. Both *Schistosomamansoni* and *Schistosoma haematobium* are found in Africa and the Middle East. These two species of schistosomes may exist separately in endemic areas or may coexist within the same region. Thus, it is not uncommon for an individual from Africa to be infected with both *S. mansoni* and *S. haematobium*. *S. mansoni* was brought to the Caribbean and South America by the slave trade in the 16th century and is now endemic. The Far Eastern species, *Schistosoma japonicum* is found primarily in China and the Philippines with a smaller focus in Indonesia. *S. japonicum* was once considered the only species of schistosome in the Far East. Recent studies indicate, however, that a second species *Schistosoma mekongi* is an important human pathogen in Laos, Cambodia, and Vietnam. *Schistosoma intercalatum* is found only in Africa; the extent of the human disease caused by this parasite is unclear (Table 1).

Figure 1. **A Case of Schistosomiasis Hematobium in a 27-Year-Old Nigerian Woman Presenting with Hematuria**

Scott Allen, MD, G. Richard Olds, MD
Brown University, Providence, RI

A twenty-seven-year-old Nigerian woman was referred to a urologist in Rhode Island following an unrevealing gynecologic workup for a two year history of blood in her urine. The patient denied any dysuria or urgency although she did report a two year history of right flank pain exacerbated by lying down. She denied any history of urinary stones, and family history for urinary disease was negative. Workup by the urologist included a routine urinalysis which showed a pH of 7.6, moderate blood, urobilinogen, moderate leukocyte esterase, 6 WBCs, 4 RBCs and few bacteria. Cystoscopy revealed "solid, pink, raised tumor to the left and below the air bubble" and "small early areas of tumor in the mid-high posterior bladder." A biopsy was obtained, and while results were pending, the patient was informed that she had bladder cancer. The subsequent pathology report revealed multiple ova of *schistosomiasis hematobium* surrounded by granulomatous inflammation.

Worldwide, the leading cause of hematuria in young adults is *schistosomiasis hematobium*. Schistosomiasis, a chronic trematode infection, affects more than 200 million people. If the diagnosis is suspected, *S. haematobium* is easily detected by examination of early or mid-day urine specimens. More important, the infection is easily treated by a single dose of praziquantel. Early detection is important because the complication of urinary obstruction leading to renal failure is often asymptomatic. In addition, untreated infection increases the risk of squamous cell carcinoma of the bladder.

Life Cycle of Schistosomes

The life cycle of all species of schistosomes exist between man, the principal definitive host, and a specific snail intermediate host. The life cycle of *S. mansoni* is shown as an example in Figure 2. In this species *S. japonicum* and *S. mekongi* as well, adult worms live in the venous system of the intestines and produce eggs that are passed out of the body into the environment through human feces. In *S. haematobium* the adult worms live in the blood supply of the urinary bladder. In this case the ova exit the body in the urine. Each female produces from 300 eggs/day for *S. mansoni* and *S. haematobium* to 3,000 eggs/day for *S. japonicum*. The egg has a protruding spine which is characteristic for each species of schistosome. Upon contact with fresh water, motile ciliated miracidia are released which locate and penetrate a specific snail intermediate host. Several weeks later, forktailed infective cercariae emerge from the snails and seek a mammalian host. Cercariae penetrate intact skin and transform into parasitic larval forms called schistosomula. The tail is left on the surface of the skin while the head penetrates and adapts to a parasitic existence within man. These larvae migrate via the blood system through the lungs, the liver and in about six weeks, mature in to egg-laying adult worms eventually residing in the venous system of choice. The mean life span of adult worms in a host is estimated to be about 5-10 years but case reports suggests that parasites may live for up to 30 years.

Clinical Syndromes

Most individuals infected with schistosomes are asymptomatic. The diagnosis may be suspected in a patient with eosinophilia or history of travel to an endemic area. Identification of characteristic eggs in stool or urine specimens may establish the diagnosis, particularly in those with heavy infections. Individuals may also develop three distinct clinical syn-

Figure 2.

LIFE CYCLE OF SCHISTOSOMA MANSONI

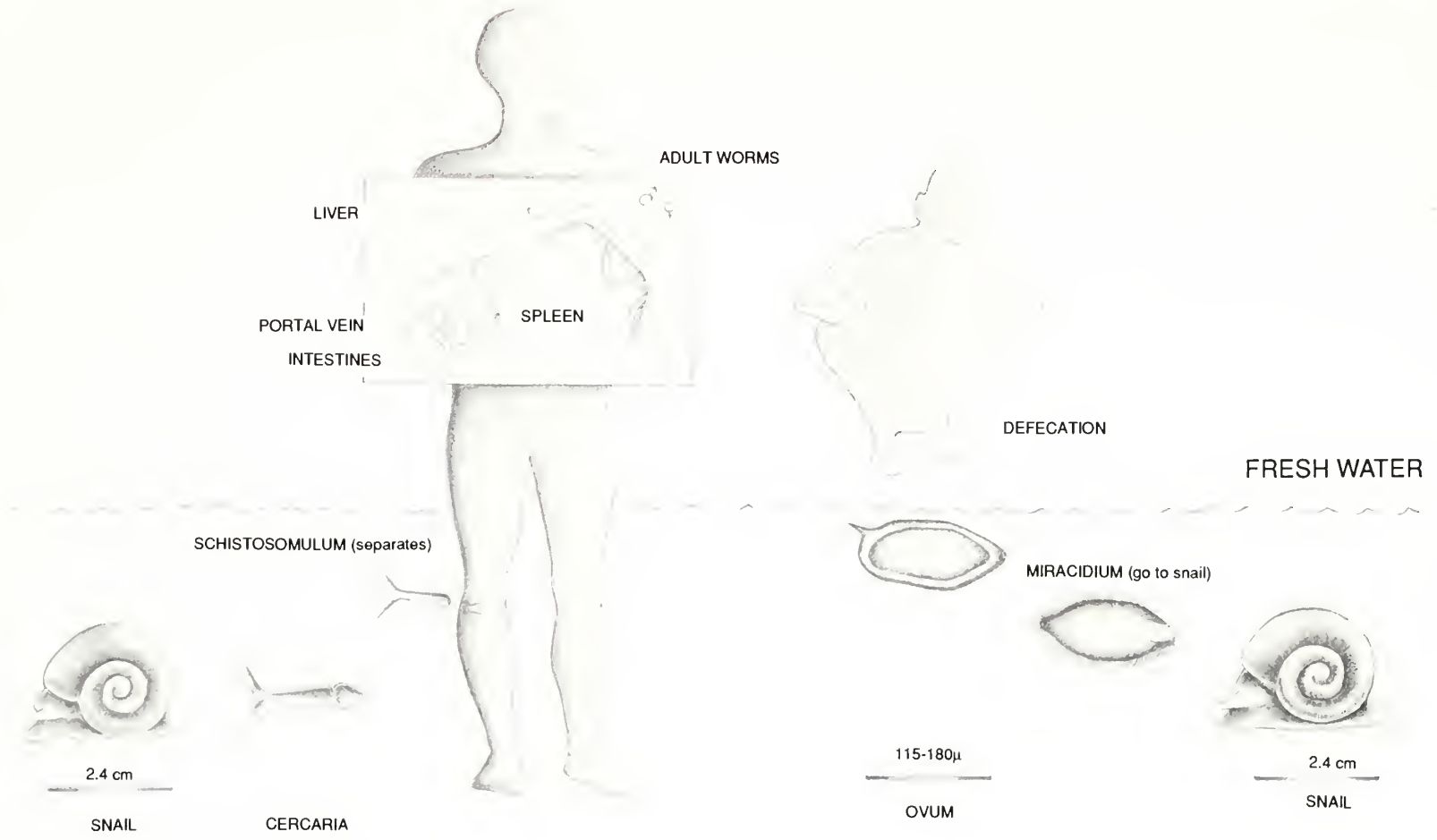


Table 1. **Schistosome Species that Infect Humans**

Species	Endemic Region	Final Habitat
S. mansoni	Middle East Africa South America Caribbean	Inferior mesenteric veins
S. japonicum	China Philippines Indonesia	Superior mesenteric veins
S. haematobium	Middle East Africa	Vesical plexus veins
S. mekongi	Cambodia Laos Vietnam	Mesenteric veins
S. intercalatum	West Africa Central Africa	Mesenteric veins

dromes depending on the time after initial worm penetration of the skin. These are cercarial dermatitis, Katayama fever and chronic schistosomiasis (Table 2).

Most individuals infected with schistosomes are asymptomatic.

Cercarial dermatitis, also known commonly as swimmer's itch, is due to skin penetration by cercariae and the subsequent death of some schistosomula within the dermis. This reaction occurs within 24 hours of exposure to cercariae and appears as a pruritic skin rash. This syndrome is rarely seen on primary exposure to schistosomes since it appears to be a sensitization to phenomenon requiring multiple exposures to cercariae and resultant schistosomula. It is usually mild and may pass unnoticed. Cercarial dermatitis is far more common when non-human (bird) cercariae penetrate skin. In this case none of the resulting schistosomula are capable of surviving in the human host and die shortly after penetration. Avian schistosomiasis is common in the Great Lake region and the Delaware Bay in the United States. In this case, the reaction is more severe with an intense inflammatory reaction within the dermis is observed.

Katayama fever occurs 4-8 weeks after cercarial penetration and coincides with the beginning of egg production. This syndrome is most commonly observed after infection with *S. japonicum* but may rarely be seen with heavy infections due to *S. mansoni*. Patients develop acute onset of fever, chills, sweating, headache and cough. Physical examination demonstrated enlargement of the liver, spleen and lymph nodes. This stage is often diagnosed as acute serum sickness but the correct etiology is generally not considered. A peripheral eosinophilia averaging about 50% is typically seen. The syndrome resolves after several weeks even without specific treatment. Unfortunately, death may occur particularly in heavy infections with *S. japonicum*. Katayama fever is, in fact a form of serum sickness believed to be due to an immune complex formation initiated by the production of egg antigens and the release of these highly antigenic molecules in to the circulation.

The most common disease syndrome produced by infections with schistosomes is chronic schistosomiasis. The pathogenesis of this syndrome is due to deposition of eggs within host tissue with elicitation of a delayed hypersensitivity granulomatous response. Later, chronic inflammation leads to deposition of a fibrous, extracellular matrix (collagen and other macromolecules) that leads to characteristic fibro-obstructive lesions of schistosomiasis. In *S. mansoni, S. japonicum* and *S. mekongi* this has been referred to as clay pipe stem fibrosis, since it resembles thick clay pipe stems thrust at diverse angles through an essentially normal liver. This pattern is quite distinctive when observed on ultrasound or abdominal CT. In intestinal schistosomiasis due to *S. mansoni* or *S. japonicum*, eggs trapped in the intestinal wall stimulate a granulomatous host response that results in the formation of polyps or bleeding ulcerations of the colon.

Katayama fever is, in fact, a form of serum sickness believed to be due to an immune complex formation initiated by the production of egg antigens and the release of these highly antigenic molecules into the circulation.

While most eggs laid by a female worm of these species pass into the intestinal tract, eggs are also carried downstream in the portal circulation to the presinusoidal spaces of the liver. The eggs lodge in the presinusoidal capillaries and induce a granulomatous host response and eventually hepatic fibrosis. A major effect of liver disease in schistosomiasis is a presinusoidal block in portal blood flow with subsequent development of portal hypertension and portal-systemic collateral circulation. Intrasplenic and portal pressures are elevated while wedge hepatic vein pressure is normal. In contrast to most other causes of cirrhotic liver diseases (ethanol, hepatitis B or C, carbon tetrachloride), hepatic function in schistosomiasis is preserved until late in the course of disease. Since patients from developing countries can be at risk for these alternative causes of hepatic diseases, some care should be taken not to conclude that portal hypertension is due to hepatitis B, for example, even

in an antigen positive patient if the patient comes from a schistosomiasis endemic country. The reverse is also true. In Egypt, for example, 30-40% of patients with pure schistosomiasis induced pathology on open biopsy are hepatitis B antigen positive. In addition, almost half the patients who were thought preoperatively to have pure schistosomal induced fibrosis also had a mixed micronodular pattern on open biopsy. In general, patients with pure cirrhotic liver disease severe enough to cause portal hypertension have small, shrunken livers. In contrast the typical patient with schistosomiasis has an enlarged liver (Figure 3). As mentioned earlier, mixed etiologies to portal obstruction unfortunately are not uncommon.

Clinically, patients infected with *S. mansoni* and *S. japonicum* infections may have nonspecific complaints such as fatigue, crampy abdominal pain or distension. Hepatomegaly may be detected primarily in the midsternal line due to enlargement of the left lobe of the liver. Splenomegaly is less commonly seen but can be massive with the spleen tip felt below the umbilicus. Splenic enlargement occurs both from passive congestion (portal hypertension) and from lymphocytic hyperplasia secondary to chronic inflammation. Intermittent episodes of hematemesis due to esophageal varices may occur. Liver function tests are usually normal. The white blood cell count is normal but with a mild degree of eosinophilia. Anemia is commonly due to chronic blood loss and hypersplenism. A small percentage of individuals will eventually develop decompensated liver disease with jaundice, ascites, liver failure, and death. This generally takes 20-30 years of chronic parasitism but can be seen in children ages 12-14 years old in endemic areas. As with other forms of fibrotic liver disease, patients with long-standing schistosomiasis are at risk to develop hepatocellular carcinoma and at least in the course of *S. japonicum* are probably at greater risk to develop colonic carcinoma. Patients with schistosomiasis are at somewhat lower risk to develop hepatic coma probably because the liver parenchyma is still intact.

Table 2. **Disease Spectrum of Schistosomiasis**

1. Cercarial dermatitis
2. Katayama fever
3. Chronic schistosomiasis
   - Hepatosplenic
   - Intestinal
   - Vesical (*S. haematobium* only)
   - Pulmonary
   - Central Nervous System

S. mekongi is a newly recognized species of schistosomes that infect humans in Southeast Asia. The parasite is closely related to *S. japonicum* but can be distinguished by the egg size and shape. Relatively little is known regarding the extent of clinical manifestations in humans by *S. mekongi*. Clinical disease is found only in a small percent of patients. Physical examination may reveal hepatosplenomegaly with associated chronic sequelae. Diagnosis is established by finding the characteristic eggs in the stools. For the purposes of this discussion it probably causes disease quite similar to *S. japonicum*.

In *S. haematobioum* infections, adult worms live in the veins surrounding the bladder. Eggs are produced that lodge within the bladder wall and lower ureters and induce granuloma formation. Patients may complain of hematuria and dysuria. Urine examination demonstrates proteinuria and hematuria. Unfortunately most patients are asymptomatic. Ultrasonography and intravenous pyelography may demonstrate hydronephrosis and bladder wall defects with calcification. These defects may resemble bladder carcinoma. Prolonged infection may lead to bilateral hydronephrosis and uremia. An association has been suggested between *S. haematobium* infection and squamous cell carcinoma of the bladder. More unusual manifestations of schistosomiasis can also be observed.

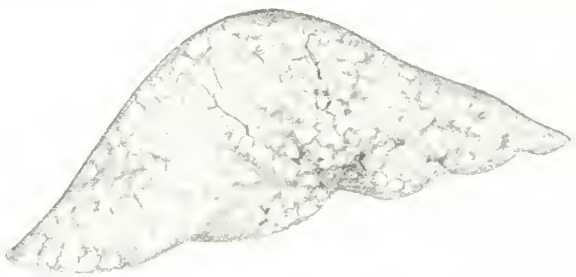
In rare cases of schistosomiasis, cor pulmonale, nephritic syndrome and transverse myelitis may occur. In addition, cerebral schistosomiasis occurs in association with *S. japonicum* infection and leads to seizures or loss of consciousness. This is probably due to migration of adult worms. Finally, infection with salmonellae in persons parasitized by any schistosome can result in the syndrome of "prolonged typhoid fever". This febrile illness may last for months with daily fever spikes. The diagnosis rests on isolating *S. typhi* or other enteric pathogens in conjunction with schistosome eggs. Persistent salmonellosis in patients with schistosomiasis may result from colonization of the parasite's surface and gastrointestinal tract with bacteria. In this location it is resistant to bacteriologic cure. In *S. haematobium* chronic infection with other salmonella species has been described. Definitive cure cannot be addressed until the schistosomes have been killed.

Diagnosis

The diagnosis of schistosomiasis is suspected in individuals with a history of travel to endemic areas. In addition, a history of contact with fresh water, skin rashes or acute febrile episodes may also suggest the diagnosis. Schistosomiasis must also be considered in the evaluation of an individual with eosinophilia. Because of the association between salmonella and schistosomes, the latter diagnosis should always be suspected in patients from areas of the world where the parasite is endemic and where the individual has recurrent or difficult to cure salmonella infection. The definitive diagnosis is dependent on finding

Figure 3.

THE LIVER



MICRONODULE
CIRRHOSIS

NORMAL

PERIPORTAL FIBROSIS
"CLAY PIPE STEM" FIBROSIS

©MARY ELIZABETH GORDON

the characteristic eggs in stool, urine or biopsy specimens. If multiple stool samples are negative and the diagnosis is still suspected, a superficial rectal biopsy may demonstrate the eggs.

Liver biopsy may also demonstrate granulomas and egg remnants but more typically shows the characteristic periportal fibrosis described earlier. The only way to definitely diagnose liver disease due to schistosomiasis is through a wedge biopsy. This approach will provide sufficient tissue to determine the presence of characteristic clay pipe stem fibrosis or granulomas due to schistosomiasis. Tissue specimens obtained from needle biopsies are usually inadequate to make a definitive diagnosis but may be useful in ruling out coincident micronodular cirrhosis (hepatitis B, C or ETOH).

Serological tests to detect anti-schistosome antibodies are available and are useful if stool and urine samples are repeatedly negative and the diagnosis of schistosomiasis is still suspected, as, for example, in cerebral schistosomiasis. It must be remembered that antibody titers may remain elevated for prolonged periods of time in individuals from endemic countries with a history of remote infection. Serology, in contrast, may be quite helpful in travelers from non-endemic countries in whom the diagnosis is suspected.

As described earlier, abdominal ultrasonography and CT scanning has recently been demonstrated to detect characteristic clay pipe stem fibrosis in the liver due to *S. mansoni* and *S. japonicum* and obstructive uropathy in *S. haematobium*. These findings along with a percutaneous biopsy free of micronodular cirrhosis could save the patient an open procedure.

Treatment

Treatment of schistosomiasis in the past was difficult since anti-schistosomal drugs were extremely toxic. Today, safe and effective oral chemotherapeutic agents are available for treatment of the major human species of schistosomes. The drug of choice is Praziquantel (Biltricide), and agent effective against all five species of schistosomes and is available in the United States. The dose is 40 mg/Kg given orally in a single dose or 50 mg/Kg in two divided AM doses for *S. mansoni* and *S. haematobium*. For infections with *S. japonicum*, Praziquantel can be given orally at a dose of 60 mg/Kg in three divided doses in a single day. Side effects are mild and include nausea, vomiting, abdominal discomfort and headache. The cure rates range from 80-95%. Dead worms may embolize to the liver or lungs following treatment and may cause transient increases in liver function test abnormality or eosinophilia. Repeated stool or urine examinations should be obtained three and six months after treatment to assure cure. Corticosteroids may be indicated for treatment of Katayama fever.

Patients with hepatosplenomegaly may benefit from treatment as evidence by reversal of organ enlargement has been clearly documented. In addition, recent studies have suggested that schistosome-induced fibrosis may also reverse. Patients presenting with complications of chronic schistosomiasis such as ascites or hematemesis should therefore be treated conservatively. Shunting of portal blood is not recommended unless recurrent bleeding becomes difficult to manage medically.

Patients with urinary tract calculi or permanent obstructive lesions secondary to *S. haematobium* may require surgical intervention.

Other drugs that can be used for treatment of schistosomiasis include metrifonate (Bayer) for *S. haematobium* and oxamniquine (Pfizer) for *S. mansoni*.

Prevention

Prevention consists of avoiding water contact in areas endemic for schistosomiasis. Swimming in fresh water in endemic areas should be avoided. Rubber boots prevent cercarial penetration of the skin. If accidental water contact occurs, rapid towelling to dry the skin or application of alcohol may prevent parasite penetration. No effective vaccine has been produced for humans and may still be years away. A skin cream to limit cercarial penetration of the skin is being developed by the military but is not commercially available as yet.

References

Chapman PJC, Wilkinson PR, Davidson RN (1988). Acute schistosomiasis (Katayama fever) among British air crew. British Medical J. 297:101.

Cheever AW (1982). Pathology pp. 742-3. In Nash TE, moderator. Schistosome infection in humans: perspective and recent findings. Ann. Int. Med. 97:740-44.

Hofstatter M, Nash TE, Cheever AW, Bustaro dos Stanos J, Ottesen EA (1981). Infection with *Schistosoma mekongi* in Southeast Asian Refugees. J. Infectious Diseases 144:420-426.

King CH, and Mahmoud AAF, 1983. Drugs five years later: Praziquantel. Ann. Internal Medicine.

Mahmoud AAF and M Farid Adbel Wahab. Schistosomiasis in Tropical and Geographical Medicine. Warren KS and Mahmoud AAF, eds. Second Edition, McGraw-Hill: New York. 1990:458-472.

MMWR. Acute Schistosomiasis in US travelers returning from Africa. 39(A):146.

Ong ELC and Ellis ME (1989). Acute Schistosomiasis (Katayama fever) Corticosteroid as Adjunct Therapy. Scand J Infect Dis 21:473-474.

Rossi CL, Tswang UCW, Picchen JB (1991). Rapid, Low Technology Field and Laboratory applicable Enzyme-linked Immunosorbent Assays for Immunodiagnosis of *Schistosoma mansoni*. J Clin Microb 29:1836-1841.

Peters PAS and Kazura JW. Update on diagnostic methods of schistosomiasis. Bailliere Clinical Tropical Medicine and Communicable Diseases 2:419-433.

Warren KS (1980). The prevalence of schistosomiasis. New England Journal of Medicine 303:203-206.

There's more to Portable X-Ray Service than X-Rays.

Yes, our main business is to provide you with fast, efficient, diagnostic X-Ray services, but we have much more to offer . . . including a staff of people who really care.

- Diagnostic X-Ray Services
- EKG
- Holter-Monitoring*
- Ultrasound Services*
- Same day reporting
- 24 Hour Service
- Seven days a week

*by appointment only

We service the entire Greater Rhode Island area:

- Nursing and Convalescent Homes
- Shut-ins and Private Home Patients
- Post Surgical Patients

PORTABLE X-RAY SERVICE

OF RHODE ISLAND

Certified by the R.I. Department of Health. Reimbursement provided by Medicare, R.I. Blue Shield and Medical Assistance.

100 Highland Avenue Providence, R.I. 331-3996	120 Dudley Street Providence, R.I. 331-3996	154 Waterman Street Providence, R.I. 273-0450	38 Hamlet Avenue Woonsocket, R.I. 766-4224

Nutritional Status and Child Growth in Schistosomiasis

Stephen T. McGarvey, PhD, MPH

In the case of developing world populations, infections with helminth parasites such as hookworm, ascaris and schistosomiasis, are important but understudied causes for the characteristic malnutrition and delayed growth.

One of the first and easiest methods to understand the general health of a population is to measure the health of children. This applies to both the obvious case of developing countries where schistosomiasis is a problem, and also to the modern industrial world. High infant and childhood mortality rates and high malnutrition rates among growing children are clear indications that a national population or ethnic sub-group within a nation is suffering some combination of poor environmental resources, limited access to preventive and curative health care and specific disease insults. Child growth monitoring is perhaps the quickest health assessment for both populations and individuals. Height or weight for age in an individual child or from a population survey can be compared to appropriate growth standards and may provide clear evidence of poor health. The next step is to determine the specific set of factors responsible for producing the poor growth performance.

Stephen T. McGarvey, PhD, MPH, is with the Program in Geographic Medicine and The International Health Institute, Brown University and Department of Medicine, The Miriam Hospital, Providence, Rhode Island.

The process of child growth in the developing world occurs in the human ecological context of an overall economic impoverishment which includes interrelated specific influences beyond parasitic diseases such as schistosomiasis. These specific factors are merely the measurable aspects of poverty in its various forms. Specific community and family socio-economic factors such as population size and density, sanitation and water systems, electrification and roadways, availability of health care, parental education and occupation, family size and land tenure are included. The specific history and ecology of the area determine the type of infectious organisms in the human environment. Community attributes mediate exposure to pathogens such as parasites, access to immunization and curative practices. Family income largely determines adequate dietary intakes of proteins and calories.

In the case of developing world populations, infections with helminth parasites such as hookworm, ascaris and schistosomiasis, are important but understudied causes of the characteristic malnutrition and delayed growth. Although intestinal worm infections are not as common in the developed world, migration from the developing to the developed world and the general mobility of late 20th century populations, may bring more children with parasitic infections into contact with Rhode Island care providers. Physicians caring for ill children who originate from, or return from visits to, such countries may want to consider the possibility of helminth infections when treating such problems as malnutrition, anemia or even growth retardation.

Despite their potential relevance for US and Rhode Island care providers, parasitism, poor nutritional status and growth interruptions remain a formidable problem in the developing world. Here we concentrate on one example of this global issue, the geohelminth parasitic infection, schistosomiasis, in order to illustrate the general problems of parasitism's health effects on children and the potential for disease control.

The purpose of this article is to briefly review the association between schistosomiasis and nutritional status and child growth. Initially, the relevant epidemiologic information is discussed, followed by the hypothetical pathophysiologic basis for such an

association. Results from our own and others' studies then are summarized. Finally, the relevance of these studies are discussed in terms of a newly developing set of ideas for schistosomiasis control programs in the developing world.

Epidemiology

The highest prevalence of schistosomiasis occurs among children and adolescents. This is the case of all Schistosoma species. Since schistosomiasis occurs after contact with infective freshwater, infections are rare in those less than 4 years of age who do not range freely outside the immediate household. Children and adolescents have the highest infection rates because of a combination of two interrelated factors. First, they probably have the greatest exposure to infective water sources compared to other ages due to their patterns of physical activity. They have the most heterogeneous exposure to water sources due to a wide geographic range within the village, adjacent agricultural fields and water sources. (Although their duration of exposure in such places as rice paddies in the Philippines is not as long as older working adults.) Second, longitudinal studies in several schistosome species suggest that immunity to reinfection develops in some individuals chronically exposed to infective water sources. This age-related development of immunity appears during or after adolescence and may account for the lower prevalence of schistosomiasis in adults (Butterworth et al 1989).

Thus, simply because of the epidemiologic patterns of schistosomiasis predominantly affecting children during the time of maximum nutritional requirements and physical growth and development, it seems reasonable to search for detrimental effects on nutrition and growth. In addition, there are several specific mechanisms due to schistosomiasis which might hypothetically influence nutritional status and growth (Stephenson 1987).

Putative Mechanisms

The final common pathway of putative mechanisms linking schistosomiasis and nutrition and growth is the decreased nutrient pool available for cellular growth and development. Any reduction in energy attributable to schistosomiasis may underlie nutritional insults and slowing of growth. There are several potential influences that decrease nutrient utilization and bioavailability. 1) Acute infections produce diarrhea and gastrointestinal bleeding and may lead to nutrient loss. 2) Acute and chronic infections seem to produce weakness and anorexia that decrease food intake. 3) The hepatomegaly of schistosomiasis may affect liver function thereby decreasing nutrient synthesis and transport. Although it appears that liver function is preserved in hepatomegaly, detailed metabolic functions studies have not been performed. 4) Splenomegaly due to schistosomiasis may affect or increase the destruction of erythrocytes.

Summary of Studies

The following section describes and summarizes results from studies on schistosomiasis and nutrition and growth of the three main schistosomes, *Schistosoma mansoni, S. haematobium*, and *S. japonicum*. They are all referenced in our recent publications on this topic (McGarvey et al 1992a, McGarvey et al 1992b) and a recent review (Stephenson 1987). Nutritional status tends to be assessed by measures of subcutaneous skinfold thickness, such as at the triceps and subscapular sites or weight for age. Physical growth is most often assessed by height or stature. No studies have yet quantified development by such pubertal stage measures as age at menarche or testicular development.

Intensity of *S. mansoni* infection and splenomegaly were associated with low height, weight and arm-muscle area in a cross-sectional study of 493 Brazilian children ages 4-14 years. This study included adjustments for the influence of a variety of socioeconomic and water use measures. In a recent study of 362 5-24 year old Kenyan school children, *S. mansoni*-related hepatomegaly was associated with reduced height- and weight-for-age, and skinfold thickness. Stephenson (1987) cites a Tanzanian study showing reduced height and weight in *S. mansoni* infected school children relative to uninfected peers. Some studies found no cross-sectional association between *S. mansoni* infection and child growth, such as a study of 138 children aged 7-16 years old from St. Lucia. Small sample sizes and low prevalence and intensity of infection may have made such effects difficult to detect in this and other inconclusive studies.

Any reduction in energy attributable to schistosomiasis may underlie nutritional insults and slowing of growth.

In a study of 786 Egyptian children ages 6 months to 10 years, those with heavy *S. haematobium* infection had significantly thinner skinfolds, as a percent of World Health Organization standards, than uninfected or more lightly infected children. However, there was no control for the potential confounding by other parasitic infections which were associated with *S. haematobium* infection. Stephenson (1987) also discusses several other studies of *S. haematobium* which must be considered inconclusive due to sample sizes, lack of control of age and intensity of infection. In a randomized treatment study of 399 Kenyan schoolchildren ages 6-16 years infected with *S. haematobium*, Stephenson and colleagues showed that metrifonate treated children had significantly greater 6-month gains in weight for age, arm circumference for age and skinfold thickness than the placebo group. Their study design controlled for differences in other parasitic infections, especially malarial, and initial nutritional status and rendered clear evidence that *S. haematobium* infection retarded growth. It would be interesting to extend this study throughout adolescence. A further randomized treatment study of 312 6-17 year old children found

that praziquantel and metrifonate both produced growth improvement over 8 months compared to placebo but that the reduction of *S. haematobium* infection intensity due to praziquantel was the most powerful influence on growth response to treatment.

Schistosoma japonicum infection and its intensity were significantly related to reduced height, arm muscle and sum of skinfolds in males and females in a cross-sectional study of 1,561 males and females aged 4-19.9 years from an endemic region of northeastern Leyte, Philippines (McGarvey et al 1992a). The greatest age-specific differences were during adolescence in both males and females with differences of 6-8 cm in height and 5-6 kilograms in weight between infected and uninfected adolescents. The growth retarding effects of schistosomiasis were significant after adjusting for the influence of other parasites, notably hookworm infection. In a similar cross-sectional study among 239 males and females aged 4-19.9 years on Jishan Island in Po Yang Lake in a highly endemic region of Jiangxi, China, current *S. japonicum* infection and intensity of infection were related to reduced height, weight, weight-for-height, and skinfold thickness in females (McGarvey et al 1992b). As in our companion Philippine study the greatest nutritional status and growth differences between infected and uninfected individuals occurred during adolescence in females. In males, intensity of schistosomiasis was related only to reduction in skinfold thickness.

Differences among schistosoma may make across species comparisons difficult as do ecological differences among the host human populations. However, it is apparent that studies which included adolescents and had large sample sizes were able to detect negative effects of schistosomiasis on nutritional status and growth measures. Further studies should also include adolescents to determine if the same effects can be found at this time of rapid growth and development. Studies which controlled for other parasites and relevant socioeconomic factors were also able to find such associations. Because most studies were cross-sectional final conclusions must be cautious. However, the one experimental study in *S. haematobium* clearly showed negative effects on nutrition and growth. We are currently conducting a similar double-blind experimental trial with *S. japonicum* in the Philippines.

A key interpretation of these studies is the reduction of growth, and potential loss of growth potential, during adolescence in the presence of schistosomiasis. This suggests that the maximum adult body size may be compromised in individuals and populations endemic for schistosomiasis. These trends, if validated, hold important implications for body-size and general health related work capabilities and economic productivity in these developing world populations.

Implications for Disease Control

The evidence of recent studies on helminth parasites, including schistosomiasis, and nutrition and growth is contributing to the consensus that the health and well-being of school-age children are disproportionately and negatively affected by such infections. This age-group may be a suitable candidate group for targeted disease control efforts (Warren et al 1992). They are easily found and treated in schools. Because of the epidemiology of infection and intensity of infection, ie, the egg burden, and their behavior patterns, they also are probably responsible for the majority of infections and their transmission. Concentrating on treating this age-group to reduce infection and morbidity and to efficiently influence transmission may be a viable option for disease control. The difficulty revolves around the decision to mass treat or screen for infections first.

One of the problems of disease control in countries with endemic schistosomiasis is the cost of screening and treatment of infected individuals. At low to moderate prevalences there may be an excessive cost of comprehensive screening for the determination of the low to moderate number of people with positive infection status and eventual treatment. In high prevalence areas, screening may be somewhat moot as a decision for treatment since upwards of 2/3 to 3/4 of all children may be infected. It should also be noted that most national control programs are currently based on a single stool exam. This probably results in missing from 10-15% of the lightly infected population (normally 2-3 stool exams give a maximum yield) even in the best hands. The actual sensitivity and specificity of these exams under existing field conditions are not currently known in most countries but in the Philippines is no more than 70%. (Under ideal conditions with expensive medical techniques this approaches 90%.)

Thus, the concept of mass treatment without prior screening becomes more attractive as policy in light of the increasing costs of screening and the realities of a single stool examination. However, two things are necessary before mass treatment becomes feasible. One, the health effects of treating uninfected individuals, mostly school-age children because of the age-specific prevalence, must be shown to be minimal. Two, the costs of the drug, most often praziquantel (see Wiest and Olds, this volume), must be low or free to offset the costs of treating uninfected individuals. Both conditions are being studied and the likelihood of trials of mass treatment is increasing.

Combining the evidence from prevalence and morbidity studies of school-age children with the potential decision to support mass treatment, the following crude outline can be proposed as a novel method of disease control and perhaps later surveillance. For control purposes, conduct mass treatment with anti-schistosomal drugs in all school-age children. Repeat this at regular intervals depending on the particular schistosome, snail host and human transmission cycle. This may require twice a year mass treatment in some areas. Conduct population studies to determine any changes in infection and morbidity after the onset of mass treatment. Continue passive

case-finding and treatment in these areas through the existing health care systems. After 2-3 years of mass treatment of school-age children and a sufficient demonstration of reduced infection and morbidity, choose a narrow age-group within school children in which regular infection and morbidity surveillance would begin. This should be the group with a maximum water contact and high infection and morbidity rates. For example, this might well be 12-15-year-old boys in most populations. Continue mass treatment but now on an annual basis, closely monitor infection rates and morbidities such as hepatosplenomegaly and nutritional and growth insults in this 'sentinel' age group. The baseline rate and their changes may provide a basis for disease surveillance and decision-making about population-level health policy concerning schistosomiasis control.

Obviously, much more detail is required to implement such ideas and plans. However, it is clear from studies of the most vulnerable age-group in schistosomiasis-endemic populations that more attention is needed to their age-specific morbidities. It is also possible that such consideration may contribute to the potential realities being discussed concerning schistosomiasis control in the developing world.

Literature Cited

Butterworth AE, Corbett EL, Dunne DW, Fulford AJC, Gachuhi RK, Klumpp R, Mbugua G, Ouma JH, Siongok TK, Sturrock RF, 1989. Immunity and morbidity in human schistosomiasis. In McAdam KP (ed), New Strategies in Parasitology. Edinburgh: Churchill, pp. 193-210.

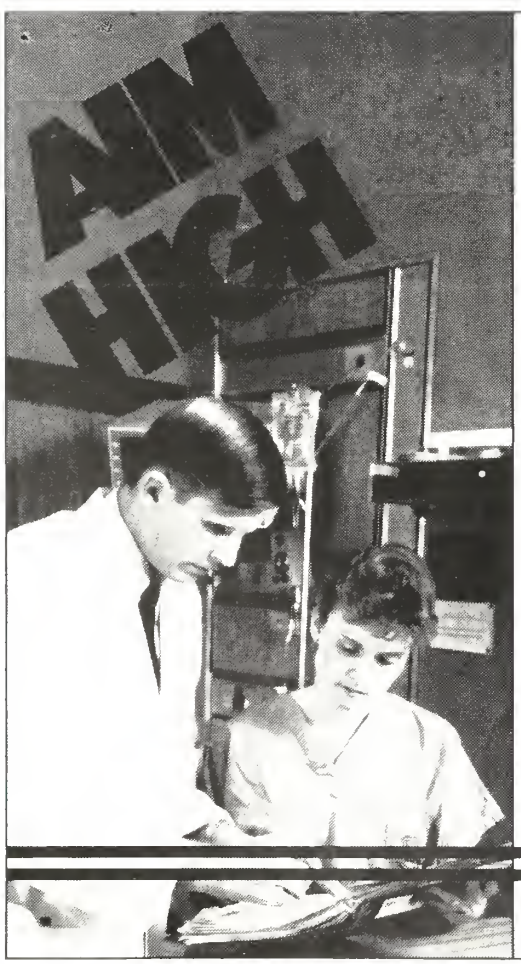
McGarvey ST, Aligui E, Daniels BD, Olveda R, Peters PA, Olds GR, 1992a. *Schistosomiasis japonica* and child growth in northeastern Leyte, Philippines I: Cross Sectional results. Am J Trop Med Hyg 46 (in press).

McGarvey ST, Wu G, Zhang S, Wang S, Peters PA, Olds GR, Wiest PD, 1992b. Nutritional status and child growth in Jiangxi, China. Trans Roy Soc Trop Med Hyg 86 (in press).

Stephenson LS, 1987. Schistosomiasis. In Stephenson LS (ed.) Impact of Helminth Infections on Human Nutrition. NY: Taylor & Francis, pp. 47-88.

Warren KS, Bundy DAP, Anderson RM, Davis AR, Henderson DA, Jamison DT, Prescott N, Senft A, 1992. Helminth Infections In Jamison DT, Mosley WH (eds.) Disease Control Priorities in Developing Countries. Washington, DC: World Bank.

Address correspondence to:
Stephen T. McGarvey, PhD, MPH
Division of Geographical Medicine
The Miriam Hospital
164 Summit Avenue
Providence, RI 02906



BE AN AIR FORCE PHYSICIAN.

Become the dedicated physician you want to be while serving your country in today's Air Force. Discover the tremendous benefits of Air Force medicine. Talk to an Air Force medical program manager about the quality lifestyle and benefits you enjoy as an Air Force professional, along with:

- 30 days vacation with pay per year
- Dedicated, professional staff
- Non-contributing retirement plan if qualified

Today's Air Force offers the medical environment you seek. Find out how to qualify. Call **USAF HEALTH PROFESSIONS** **TOLL FREE 1-800-423-USAF**

AIR FORCE

Cytokines, Hepatic Fibrosis and Schistosomiasis

Thomas F. Kresina, PhD
Quing He, MD, PhD
Mark A. Zern, MD

A complex network of soluble factors or cytokines coordinate the activation/suppression of differing cells and tissues within the body.

There are two great immunologic questions in schistosomiasis research: 1) How do humans protect themselves from parasitic invasion? and 2) once infected why do only a percentage of infected hosts go on to get clinical disease? The former question is used to develop vaccines against infection and was discussed in this monograph by Drs Knopf and Suri. The latter involves the immunopathogenesis of schistosomiasis and will be briefly reviewed here.

If no one became ill following schistosome infection it would be fair to say that few would be interested in studying this parasite. The most successful parasites in fact are those that cause little or no clinical disease since any shortening of the survival of the infected host ultimately destroys the home for the parasite. In this regard the schistosome is only moderately successful.

The basic unit of pathology in all forms of schistosomiasis is the granulomatous host immune response which forms around schistosome eggs trapped in the host tissues. This is a dead-end for the parasite, since these ova cannot contribute to the maintenance of the life cycle and the chronic inflammatory response is detrimental to the host. About a third of eggs produced by an adult worm pair suffer this fate. Although any infected individual will have egg granulomas, some individuals appear to deal with this infection better than others.

Faced with the inability to destroy the adult worms, the only option facing the host is to limit tissue damage modulating or down regulating these inflammatory reactions to a point where the trapped ova are destroyed but at a minimum of host tissue destruction. This type of adjustment is the hallmark of chronic parasitism. The fact that only a third of chronically infected patients go on to develop severe hepatosplenic disease is a testament to how effective this process is on a population basis. Still the subset of the infected population which develop overt clinical disease represents between 50 and 100 million individuals worldwide and it is estimated that approximately 1% of the infected population die each year from the direct or indirect chronic manifestations of the disease.

Parasite eggs are able to dissect through tissue plane on these attempts to exit the body by releasing toxic enzymes ahead of them. These molecules (soluble egg antigens) are unfortunately highly immunogenic and form the molecular basis for host inflammation. They induce a largely delayed type hypersensitivity reaction (DTH) and ultimately large egg granulomas form.These foci of inflammation however resolve with ova destruction but in their place is left a fibrous scar. Thus our understanding

Thomas F. Kresina, PhD, is Associate Professor of Medicine, International Health Institute, Brown University, Providence, Rhode Island.

Quing He, MD, PhD, is a visiting scholar at the International Health Institute, Brown University, Providence, Rhode Island.

Mark A. Zern, MD, is Associate Professor of Medicine, International Health Institute, Brown University, Providence, Rhode Island.

ABBREVIATIONS USED:
DNA: deoxyribose nucleic acid
DTH: detailed type hypersensitivity
IL1: interleukin-1
TNF: tumor neurosis factor
TGF-B: transforming growth factor B1
MRNA: messenger ribose nucleic acid

of this process is not restricted to regulation of DTH but to understanding the link between DTH and subsequent fibrosis. This latter point is particularly relevant since it is hepatic fibrosis which we see at autopsy in chronically infected humans who develop clinical disease rather than massive granulomatous inflammation.

Much of our understanding of this process and its regulation has come from the characterization of a variety of cell hormones called cytokines which are now thought to mediate this process *in vivo*.

Cytokines

A complex network of soluble factors or cytokines coordinate the activation/suppression of differing cells and tissues within the body. These mediators are components in maintaining or restoring physiological homeostasis.[1-3] The cytokines are a heterogeneous group of proteins produced by a variety of cells that induce similar synergistic, distinct or antagonistic signals. Common characteristics of these mediators include: 1) glycoprotein composition of less than 80,000 daltons, 2) transient cellular production in small quantities with effective local concentration in the picomole range, 3) short biological half lives, 4) binding of high affinity cell surface receptors specific for each cytokine, and 5) paracrine or autocrine actions with local cellular effects. Cytokines may be synthesized and secreted by multiple cell types including monocytes, lymphocytes, neutrophils, fibroblasts, endothelial cells, smooth muscle cells and epithelial cells. Some of the pleiotropic biological effects of a representative group of cytokines are summarized in Table 1. The summary information of Table 1 shows that cytokines are multifunctional in their biological effects. Thus the question arises – How can these mediators act in a precise fashion in a tissue system? It could be imagined that a seemingly bewildering array of cytokines and thus cytokine interactions could arise in a complex tissue with multiple cell types which are in a dynamic state of cellular flux. However, cytokines may function at two levels: the first as intercellular regulators of gene expression and secondly as intracellular regulators through second messenger pathways.[4,5] Thus specific levels of regulation of cytokine expression and function occur. This regulation can be through direct cytokine effects on the expression of other cytokines, via cytokine receptor expression modulation or by transcriptional control via specific transcription factors (ie, DNA binding proteins). Cells therefore respond to the extensive panel of cytokines expressed autocrinely or paracrinely though the synthesis of specific cell surface receptor(s) and transcriptional activation factor(s).

Table 1. **Biological Properties of Cytokines**

Cytokines	Properties
IL-1	Augment collagen and fibronectin production. Stimulate release of lytic enzymes and prostaglandin E_2. Induce acute phases reactants. Stimulate IL-2 synthesis and IL-2R Chemotactic for T lymphocytes.
IL-2	T-cell maturation factor. Up regulate IL-2 receptor. Simulate production of B cell growth factors. Activation of NK cells.
IL-3	Colony stimulating factor.
IL-4	Modulates activation and differentiation of lymphoid cells. Antagonist to IL-2 autocrine for specific T cells. Promotes IgE response.
IL-5	B-cell differentiation factor.
IL-6	T-cell activation and differentiation factor. Promotes B cells to antibody producing cells. Promotes IL-2 and IL-2R expression. Hybridoma growth factor. Induction of hepatic acute phase response.
TNF-α	Similar biological effects to IL-1 including induction of collagenase and PGE_2. Increase neutrophil adhesion. Stimulate bone resorption. Suppress Type I collagen gene expression.
γ-INF	Inhibit collagen synthesis. Increase MHC antigen expression and fibronection transcription.
GM-CSF	Enhances TNF-α and IL-1 synthesis and colony stimulating factor.
TGF-B	Inhibits IL-2 dependent T-B lymphocyte proliferation and antibody secretion. Promotes collagen gene expression. Promotes granulation tissue *In Vivo*.

Cytokines and Hepatic Fibrosis

The liver is a central organ which plays a significant role in the defense of microbial infection and neutralization of toxic agents. This serves to maintain a homeostatic state after the induction of stress. In this regard, the cytokine interleukin-1 (IL1), tumor neurosis factor -α (TNF) - α and IL-6 have been reported to mediate changes in hepatic metabolism due to injury/insult.[5] This is thought to occur through the augmentation of acute phase proteins. These acute phase proteins include c-reative protein, serum amyloid A, heptoglobulin and α 1 antichymotrypsin, fibrinogen, α 1 antitrypsin, α 1 acid glycoprotein, ceruloplasmin and complement factor B.[1] The numerous interactions of some cytokines in hepatic metabolism are summarized in Table 2.

Table 2. **Cytokines and Hepatic Metabolism**

Metabolism	Cytokine
Amino acid and protein	IL-6, IL-1, TNF, TGF-B
Mineral	IL-1, IL-6, TNF, INF
Lipid	TNF, IL-1, INF
Carbohydrate	IL-6, IL-1
Endocrine	IL-1, TNF, INF
Acute Phase Protein	IL-6, IL-1, TNF, TGF-β

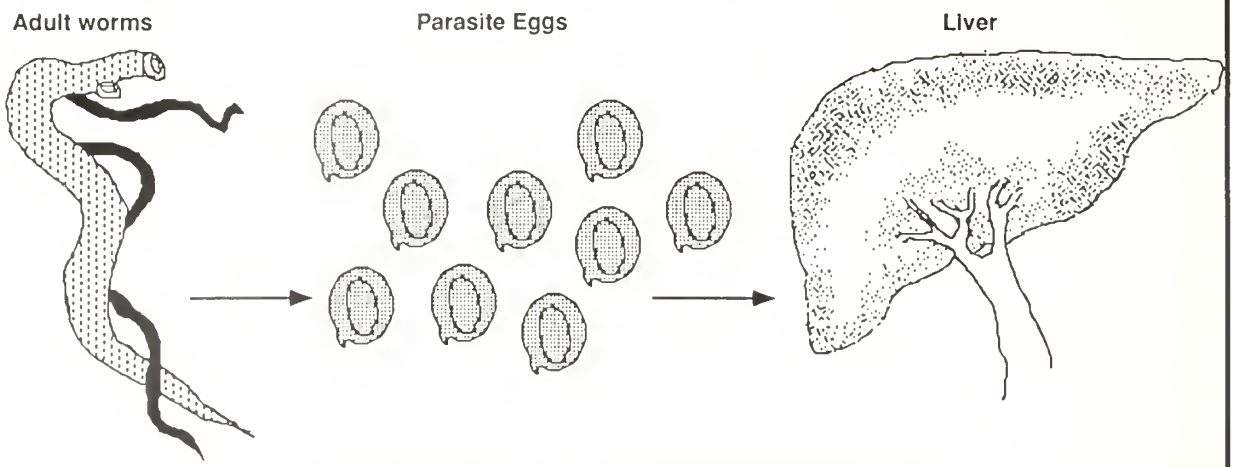
The liver can act as a clearance organ as well as a synthesizer of cytokines. For example, circulating cytokines IL-1, IL-3, IL-6, TNF-α, TGF-B, and γ - INF have all been shown to be cleared from the plasma through the liver. In disease states, which include hepatic fibrosis, a lack of liver clearance function could result in aberrant immune response profiles through augmented serum cytokine levels.

Cytokines, Liver Fibrosis and Schistosomiasis

Hepatic fibrosis is the most important clinical sequelae of chronic infection with the parasite *Schistosoma japonicum* and *Schistosoma mansoni*.[9] Pathologically, the infected livers show a granulomatous inflammatory response around parasite eggs in portal sinusoids and dense bands of extracellular collagen periportally. Most infected individuals have some degree of hepatic fibrosis and between 5-30% of the 300 million persons infected worldwide have significant hepatic fibrosis that results in clinical disease.[10] Hepatic fibrosis in schistosomiasis is extensive in the intrahepatic portal channels causing obstruction of portal venous flow. If unresolved, this hepatic involvement can clinically manifest itself as bleeding esophageal varices, the major morbid sequela. One novel feature of schistosome-induced liver disease is that the liver parenchyma remains largely intact until very late. Thus in contrast to all other forms of fibrotic liver disease(cirrhotic disease) liver synthetic function is maintained. Thus schistosomiasis is a purely mechanical obstruction of portal blood flow. In fact if the fibrous macromolecules could be removed one would be left with an essentially normal liver. Another novel feature of schistosomal liver disease is that significant resolution of liver fibrosis can be observed in children and acutely infected animal models of schistosomiasis following parasitologic cure. In this resolution, there is an immunologically mediated manipulation of hepatic fibrosis. Hepatic granuloma collagen content and biosynthesis is also observed.[12,13] The role of cytokines in this process is currently being evaluated. The emerging picture appears to be a complex interaction of numerous cytokines expressed during different stages of infection, which in turn modulate different host responses to the parasite. Recent studies indicate that IL-2 is a necessary cytokine to develop the granulomatous inflammation which surrounds the parasitic eggs.[14,15] Acute phase proteins, especially α2-macroglobulin, appear to augment established hypersensitivity responses.[16] For the maintenance of these granulomatous responses IL-1 and TNF appear to be more prominent. Soluble egg antigens, shed from hepatic eggs appear to be the major stimulus for IL-4 and IL-5 production in the granuloma.[18] The production of IL-4 and IL-5 are also required for the blood and tissue eosinophilia and IgE response.[19,20] But not all cytokines involved in inflammation are important mediators of fibrosis. This correlates with the observation in animals that there is no systematic relationship between size of granulomatous inflammation and subsequent fibrosis *per se* and then these two processes appear to be under independent immunologic control. In this regard schistosomal egg granulomas have recently been shown to produce factors, presumably cytokines, in acute infection which promote fibrogenesis;[21] these undetermined mediators are not evident in chronic infection. Modulation of these mediators of inflammation and fibrosis are thought to form the basis for the modulation of disease observed during chronic parasitism. Given our understanding of the fibrotic processes observed in the liver in other disease states, research has focused on other fibrogenic cytokines including TGF-B, IL-1 and TNF-α. These in fact are maximally present during acute infection and decrease over time in chronic disease.

In general, modulation of fibrosis in humans is considerably slower than inflammation. In humans with *S.*

Figure 1. **Cytokine involvement in Schistosomal-induced Hepatic Fibrosis**



Time Course of Murine Schistosomiasis Infection

Stage	Acute	Maintainance	Chronic
Weeks Post Infection	1-8	8-15	15-30
Cytokines	Acute Phase Proteins IG - 2 TGF - ß	IL- 1 TNF IL- 4 IL- 5	UNKNOWN

Japonicum, for example, hepatic enlargement (mostly caused by granulomatous inflammation) peaks in human populations chronically infected with this parasite at age 15-20 and subsequently resolves despite continued parasitism. These same individuals do not down-regulate ongoing fibrosis (manifest by fragments of type III collagen) until 35-40 years of age. As shown in Figure 1, numerous cytokines appear at various time points during the course of chronic murine schistosomiasis. Thus the appearance of an orchestrated cascade of cytokine is needed as part of the successful host response to helminth-induced infection. Less is known about this process in man except that it plays itself out over decades rather than months as in the mouse.

If this process can not be regulated or is maintained throughout parasitism at the level observed during acute infection, it is theorized that severe pathology develops quickly. This is consistent with the observation that death from severe hepatosplenic disease is most commonly observed in the 13-30 age group or roughly 10 years into the natural history of parasitic infection. Fortunately, most individuals adjust and limit this process but still slowly develop significant fibrotic changes in the liver over the next several decades. Thus in schistosomiasis endemic areas of the world most individuals die with schistosomal-induced hepatic fibrosis rather than as a direct result of it.

How this process will be changed by the introduction of successful chemotherapy (Praziquantel) is unknown. When treatment is delivered often (every year) and coverage is high it will undoubtedly have a very positive impact on limiting fibrosis, particularly in children. If, however, population-based control is incomplete, treatment sporadic, and coverage thin, then the potential exists for treatment to interfere with the natural adaptation of the host to chronic infection. This theoretically could lead to enhanced cytokine production observed during acute infection for longer periods of time since the typical individual with schistosomiasis would have frequent acute infections rather than chronic infestations. This might result in an increase rather than a decrease in morbidity including hepatic fibrosis.

These questions remain as yet unanswered but are the basis for a great deal of current research. If we could mimic the adjustments observed in

chronically-infected individuals (those who successfully modulated) then it might be possible to develop a vaccine to limit pathology even in those who are frequently reinfected. Such an "anti-pathology" vaccine is a unique concept in infection control but currently the ultimate goal for investigation studies this part of the immune reaction to schistosomes.

References

[1] Andus T, Bauer J, Gerok W. Effects of Cytokines on the Liver. Hepatology 13:364-375, 1991.

[2] Caerkinsky C, Anderson G, Ferruya B, et al. Detection of Human Cytokine-Secreting Cells in Distinct Anatomical Compartments. Immunol Reviews 119:5-22, 1991.

[3] Balkwell FR, Burke F. The Cytokine Network. Immunol Today 10:299-304, 1989.

[4] Torey MG. Expression of the Genes of Interferon and Other Cytokines in Normal and Diseased Tissues of Man. Experimentia 45:526-535, 1989.

[5] Kovacs EJ. Control of IL-1 and TNF-2 Production at the Level of Second Messenger Pathways. In Kimball ES (ed) Cytokines and Inflammation. CRC Press, 1991, pp. 89-107.

[6] Czeja MJ, Weinter FR, Flanders KC, et al. *In Vitro* and *In Vivo* Association of Transforming Growth Factor-Beta 1 with Hepatic Fibrosis. J Cell Biol 108:2477, 1989.

[7] Weiner RW, Giambrone MA, Czeja MJ, et al. Ito Cell Gene Expression and Collage Regulation. Hepatology 11:111-117, 1990.

[8] Masuoka M, Pham NT, Tsakamoto H. Differential Effects of Interleukin-1, Tumor Necrosis Factor and Transforming Growth Factor on Cell Proliferation and Collagen Formation by Cultured Fat-Storing Cells. Liver 9:71-78, 1989.

[9] Dunn MA, Kamel R. Hepatic Schistosomiasis. Hepatology 1:643-661, 1981.

[10] Doming EO, Tiu E, Peter PA, et al. Morbidity in *Schistosomiasis japonica* in Relation to Intensity of Infection – A Study of a Community in Leyte, Philippines. Am J Trop Med Hyg 29:858-67, 1980.

[11] Warren KS. The Influence of Treatment on the Development and Course of Murine Hepatosplenic *Schistosomiasis mansoni*. Trans. Roy Soc Trop Med Hyg 56:510-519, 1972.

[12] Olds GR, Stavitsky AB. Mechanism of *In Vivo* Modulation of Granulomatous Inflammation in Murine *Schistosomiasis japonicum*. Infect Immun 52:513-518, 1986.

[13] Olds GR, Kresina TF. Immunoregulation of Hepatic Fibrosis in Murine *Schistosomiasis Japonica*. J Inf Dis 159:798-801, 1989.

[14] Mathew RC, Ragheb S, Boros DL. Recombinant IL-2 Therapy Reverses Diminished Granulomatous Responsiveness in Anti L3T4 Treated *Schistosoma mansoni*-Infected Mice. J Immunol 144:4356-4361, 1990.

[15] Kresina TF. *In Vivo* Regulation of *S. Japonica* Granuloma Formulation by an IL-2 Antagonist. Parasitology 102:243-250, 1991.

[16] Van Cool J, Van Tiel D, Doenhodd MJ, Van Vogt H. Effect of Acute Phase Proteins, Especially α2-Macroglobulin, on Granuloma Formation around *Schistosoma mansoni* Eggs in the Rat. Parasitology 102:49-56, 1991.

[17] Chensue SW, Otterness IG, Higaski, GI. Monokine Production by Hypersensitivity (*Schistosoma mansoni* Eggs) and Foreign Body (Sephadex Bead) Granuloma Macrophages. J Immunol 142:281-287, 1988.

[18] Grych JM, Pearce E, Cheever A. Egg Deposition is the Major Stimulus for the Production of the Cytokines in Murine *Schistosomiasis mansoni*. J Immunol 146:1322-1327, 1991.

[19] Sher A, Coffman RL, Hieny S, et al. Interleukin-5 is Required for the Blood and Tissue Eosinophilia but not Granuloma Formation Induced by Infection with *Schistosoma mansoni*. Proc Natl Acad Sci USA 87:61-65, 1990.

[20] Finkelman FD, Pearce EJ, Urban JF, Sher A. Regulation and Biological Function of Helminth-Induced Cytokine Response. Immunol Today A62-66, 1991.

[21] Prakash S, Postlewaite AE, Eyler DJ. Alteration in Influence of Granuloma-Derived Cytokines on Fibrogenesis in the Course of Murine *Schistosoma mansoni* Infection. Hepatology 13:970-976, 1991.

Address correspondence to:
Thomas F. Kresina, PhD
Department of Medicine
The Miriam Hospital
164 Summit Avenue
Providence, RI 02906

RHODE ISLAND

Excellent opportunities in urgent care facilities for career oriented physicians. Competitive salary and benefits.

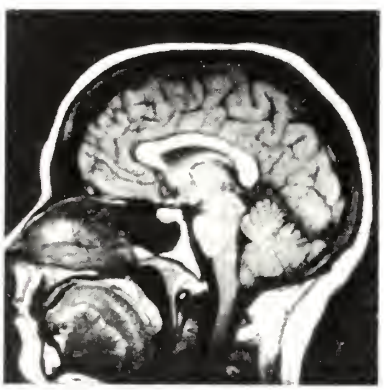
(401) 943-4540

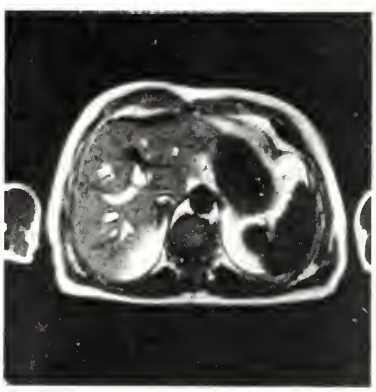
or send CV to:

Anthony Migliaccio, MD
Medical Director
Northeast Health Care, Inc.
495 Atwood Avenue
Cranston, RI 02920

RI-MASS MRI, P.C. is pleased to sponsor the

2ND WEDNESDAY LECTURE SERIES





WHEN: The 2nd Wednesday
of each month
6:30 p.m. - 7:30 p.m.

WHERE: Marriott Hotel
Charles at Orms
Providence, RI 02904

THIS MONTH'S TOPIC:
"MRI of Cerebrovascular Disease"
Wednesday, April 8, 1992

NEXT MONTH'S TOPIC:
"MRI of White Matter Disease"
Wednesday, May 13, 1992

TO REGISTER/CALL: 1 (800) 848-9661

NURSING PLACEMENT
HOME CARE INC.

"The 1st Choice in Certified Home Health Agencies"

We Are Proud To Announce:

NURSING PLACEMENT HOME CARE, INC.,
a **MEDICARE** and **MEDICAID CERTIFIED AGENCY.**

NPHC, the only letters that define Quality and Dependable Home Health Care in RI. Your patients deserve a choice and **NPHC** can offer them that – with a complete range of care options from Home Health Aides to Registered Nurses and all therapies.

We have provided your hospitals and private patients with quality care for 15 years and are now certified to serve all homebound patients in Rhode Island.

- RN assessments
- 24 hr. supervision
- RN
- HHA
- PT
- OT
- Speech
- MSW
- IV Therapy
- Pediatrics

"For Home Care You Can Rely On"

NPHC

Please call 453-4474
1-800-287-2940

ONLY ONE H_2-ANTAGONIST HEALS REFLUX ESOPHAGITIS AT DUODENAL ULCER DOSAGE. ONLY ONE.

Of all the H_2-receptor antagonists, only Axid heals and relieves reflux esophagitis at its standard duodenal ulcer dosage. Axid, **150** mg b.i.d., relieves heartburn in **86%** of patients after one day and **93%** after one week.[1]

AXID®
nizatidine
150 mg b.i.d.

ACID TESTED. PATIENT PROVEN.

1. Data on file, Lilly Research Laboratories

See accompanying page for prescribing information

© 1991 ELI LILLY AND COMPANY

NZ-2947-B-249304

AXID®
nizatidine capsules

Brief Summary Consult the package insert for complete prescribing information.

Indications and Usage: 1. *Active duodenal ulcer*—for up to 8 weeks of treatment at a dosage of 300 mg h.s. or 150 mg b.i.d. Most patients heal within 4 weeks.

2. *Maintenance therapy*—for healed duodenal ulcer patients at a dosage of 150 mg h.s. at bedtime. The consequences of therapy with Axid for longer than 1 year are not known.

3. *Gastroesophageal reflux disease (GERD)*—for up to 12 weeks of treatment of endoscopically diagnosed esophagitis, including erosive and ulcerative esophagitis, and associated heartburn at a dosage of 150 mg b.i.d.

Contraindication: Known hypersensitivity to the drug. Because cross sensitivity in this class of compounds has been observed, H_2-receptor antagonists, including Axid, should not be administered to patients with a history of hypersensitivity to other H_2-receptor antagonists.

Precautions: *General*—1. Symptomatic response to nizatidine therapy does not preclude the presence of gastric malignancy.

2. Dosage should be reduced in patients with moderate to severe renal insufficiency.

3. In patients with normal renal function and uncomplicated hepatic dysfunction, the disposition of nizatidine is similar to that in normal subjects.

Laboratory Tests—False-positive tests for urobilinogen with Multistix® may occur during therapy.

Drug Interactions—No interactions have been observed with theophylline, chlordiazepoxide, lorazepam, lidocaine, phenytoin, and warfarin. Axid does not inhibit the cytochrome P-450 enzyme system; therefore, drug interactions mediated by inhibition of hepatic metabolism are not expected to occur. In patients given very high doses (3,900 mg) of aspirin daily, increased serum salicylate levels were seen when nizatidine, 150 mg b.i.d., was administered concurrently.

Carcinogenesis, Mutagenesis, Impairment of Fertility—A 2-year oral carcinogenicity study in rats with doses as high as 500 mg/kg/day (about 80 times the recommended daily therapeutic dose) showed no evidence of a carcinogenic effect. There was a dose-related increase in the density of enterochromaffin-like (ECL) cells in the gastric oxyntic mucosa. In a 2-year study in mice, there was no evidence of a carcinogenic effect in male mice, although hyperplastic nodules of the liver were increased in the high-dose males as compared with placebo. Female mice given the high dose of Axid (2,000 mg/kg/day, about 330 times the human dose) showed marginally statistically significant increases in hepatic carcinoma and hepatic nodular hyperplasia with no numerical increase seen in any of the other dose groups. The rate of hepatic carcinoma in the high-dose animals was within the historical control limits seen for the strain of mice used. The female mice were given a dose larger than the maximum tolerated dose, as indicated by excessive (30%) weight decrement as compared with concurrent controls and evidence of mild liver injury (transaminase elevations). The occurrence of a marginal finding at high dose only in animals given an excessive and somewhat hepatotoxic dose, with no evidence of a carcinogenic effect in rats, male mice, and female mice (given up to 360 mg/kg/day, about 60 times the human dose), and a negative mutagenicity battery are not considered evidence of a carcinogenic potential for Axid.

Axid was not mutagenic in a battery of tests performed to evaluate its potential genetic toxicity, including bacterial mutation tests, unscheduled DNA synthesis, sister chromatid exchange, mouse lymphoma assay, chromosome aberration tests, and a micronucleus test.

In a 2-generation, perinatal and postnatal fertility study in rats, doses of nizatidine up to 650 mg/kg/day produced no adverse effects on the reproductive performance of parental animals or their progeny.

Pregnancy—Teratogenic Effects—Pregnancy Category C—Oral reproduction studies in rats at doses up to 300 times the human dose and in Dutch Belted rabbits at doses up to 55 times the human dose revealed no evidence of impaired fertility or teratogenic effect, but, at a dose equivalent to 300 times the human dose, treated rabbits had abortions, decreased number of live fetuses, and depressed fetal weights. On intravenous administration to pregnant New Zealand White rabbits, nizatidine at 20 mg/kg produced cardiac enlargement, coarctation of the aortic arch, and cutaneous edema in 1 fetus, and at 50 mg/kg, it produced ventricular anomaly, distended abdomen, spina bifida, hydrocephaly, and enlarged heart in 1 fetus. There are, however, no adequate and well-controlled studies in pregnant women. It is also not known whether nizatidine can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. Nizatidine should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nursing Mothers—Studies in lactating women have shown that 0.1% of an oral dose is secreted in human milk in proportion to plasma concentrations. Because of growth depression in pups reared by treated lactating rats, a decision should be made whether to discontinue nursing or the drug, taking into account the importance of the drug to the mother.

Pediatric Use—Safety and effectiveness in children have not been established.

Use in Elderly Patients—Healing rates in elderly patients were similar to those in younger age groups as were the rates of adverse events and laboratory test abnormalities. Age alone may not be an important factor in the disposition of nizatidine. Elderly patients may have reduced renal function.

Adverse Reactions: Worldwide, controlled clinical trials included over 6,000 patients given nizatidine in studies of varying durations. Placebo-controlled trials in the United States and Canada included over 2,600 patients given nizatidine and over 1,700 given placebo. Among the adverse events in these placebo-controlled trials, only anemia (0.2% vs 0%) and urticaria (0.5% vs 0.1%) were significantly more common in the nizatidine group. Of the adverse events that occurred at a frequency of 1% or more, there was no statistically significant difference between Axid and placebo in the incidence of any of these events (see package insert for complete information).

A variety of less common events were also reported; it was not possible to determine whether these were caused by nizatidine.

Hepatic—Hepatocellular injury (elevated liver enzyme tests or alkaline phosphatase) possibly or probably related to nizatidine occurred in some patients. In some cases, there was marked elevation (>500 IU/L) in SGOT or SGPT and, in a single instance, SGPT was >2,000 IU/L. The incidence of elevated liver enzymes overall and elevations of up to 3 times the upper limit of normal, however, did not significantly differ from that in placebo patients. All abnormalities were reversible after discontinuation of Axid. Since market introduction, hepatitis and jaundice have been reported. Rare cases of cholestatic or mixed hepatocellular and cholestatic injury with jaundice have been reported with reversal of the abnormalities after discontinuation of Axid.

Cardiovascular—In clinical pharmacology studies, short episodes of asymptomatic ventricular tachycardia occurred in 2 individuals administered Axid and in 3 untreated subjects.

CNS—Rare cases of reversible mental confusion have been reported.

Endocrine—Clinical pharmacology studies and controlled clinical trials showed no evidence of anti-androgenic activity due to nizatidine. Impotence and decreased libido were reported with similar frequency by patients on nizatidine and those on placebo. Gynecomastia has been reported rarely.

Hematologic—Anemia was reported significantly more frequently in nizatidine than in placebo-treated patients. Fatal thrombocytopenia was reported in a patient treated with nizatidine and another H_2-receptor antagonist. This patient had previously experienced thrombocytopenia while taking other drugs. Rare cases of thrombocytopenic purpura have been reported.

Integumental—Urticaria was reported significantly more frequently in nizatidine- than in placebo-treated patients. Rash and exfoliative dermatitis were also reported.

Hypersensitivity—As with other H_2-receptor antagonists, rare cases of anaphylaxis following nizatidine administration have been reported. Rare episodes of hypersensitivity reactions (eg, bronchospasm, laryngeal edema, rash, and eosinophilia) have been reported.

Other—Hyperuricemia unassociated with gout or nephrolithiasis was reported. Eosinophilia, fever, and nausea related to nizatidine have been reported.

Overdosage: Overdoses of Axid have been reported rarely. If overdosage occurs, activated charcoal, emesis, or lavage should be considered along with clinical monitoring and supportive therapy. The ability of hemodialysis to remove nizatidine from the body has not been conclusively demonstrated, however, due to its large volume of distribution, nizatidine is not expected to be efficiently removed from the body by this method.

PV 2093 AMP [101591]

Additional information available to the profession on request

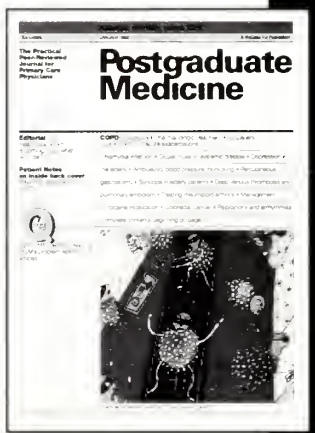
Lilly

Eli Lilly and Company
Indianapolis, Indiana
46285

NZ-2947-B-249304

© 1991, ELI LILLY AND COMPANY

US THEM



WHEN YOU NEED TIME ON YOUR SIDE, THE CHOICE IS CLEAR.

NO CLINICAL CLUTTER—PGM ARTICLES ARE CLEAR, CONCISE, WELL ILLUSTRATED, AND PRACTICAL.

Postgraduate Medicine

Modern Approaches to Development of Vaccines Against Schistosomes

Paul M. Knopf, PhD
Parmjeet K. Suri, PhD

Vaccination, as currently practiced, is a prophylactic procedure. A vaccine is given before exposure to the infectious agent, in order to induce a state of specific immunological memory within the recipient.

Introduction

Advantages of Vaccination Strategies

The development of vaccines against the human schistosome species has progressed rapidly over the past 10-15 years and there could be an effective product by the end of this century. Our essay presents some highlights of this achievement, in the context of reviewing developments in the fields of immunology, molecular biology, and cellular technology that have contributed significantly to this rapid progress.

Vaccination, as currently practiced, is a prophylactic procedure. A vaccine is given before exposure to the infectious agent, in order to induce a state of specific immunological memory within the recipient. Recalling this memory, following exposure to the authentic infectious agent, leads to a more rapid, and potent, specific immune response which effectively eliminates the infectious agent before it has progressed to the stage of causing overt disease. In the case of an infectious agent which has a long lifetime within a previously unimmunized host, and/or in which the disease only develops gradually, it is conceivable to imagine post-infection strategies which eliminate the infectious agent or minimize the pathology, by modifying the immune response. Such strategies are called immunotherapeutic or immunomodulatory, in contrast to the more classical immunoprophylactic strategies which are employed. In the case of schistosomiasis, both strategies are being considered.

Events occurring within lymphoid organs which induce a state of immunological memory, as well as events which lead to production of effector phase components of the immune response that eliminate the infection (ie, antibodies, cytolytic T lymphocytes, or activated effector T lymphocytes secreting a variety of cytokines), are being understood at increasing levels of sophistication. Immunologists have been encouraged to reconsider development of vaccines against parasites that have thus far proven refractile to earlier efforts. Moreover, the modern technical achievements of genetic engineering and cell cloning afford the opportunity to identify specific parasite components for vaccines and to prepare them in large quantities for mass immunizations at greatly reduced expense. This is particularly relevant in schistosomiasis since the populations most affected are among the poorest citizens on our planet.

Most persons who become infected with schistosomes, by repeated exposure to low doses of cercariae, do not develop clinical symptoms for several years. Significant pathology may occur before symptoms are sufficient to cause the subject to seek medical help. When the cause of their problems is correctly diagnosed, highly effective drugs are currently available for treatments which eliminate the adult

Paul M. Knopf, PhD, is Professor of Medical Science, Section of Molecular, Cellular & Developmental Biology, Division of Biology and Medicine, Brown University, Providence, Rhode Island.

Parmjeet K. Suri, PhD, is Research Associate, Section of Molecular, Cellular & Developmental Biology, Division of Biology & Medicine, Brown University, Providence, Rhode Island.

ABBREVIATIONS USED:
ARMs: antigen recognition molecules
ADCC: antibody-dependent cellular cytotoxicity
cDNA: complementary DNA
MoAbs: monoclonal antibodies
mRNA: messenger ribose nucleic acid

worms. To a large extent, however, the cured subjects in endemic areas become re-infected. Moreover, the reversal of the pathology is slow and probably incomplete, even if reinfection is absent. A more sensitive diagnostic procedure, able to detect infection before the symptoms of the disease appear, is desirable and simple, rapid immunological techniques may soon be available. Even if detection is improved, there are concerns over the potential genetic selection of worms resistant to the current drugs. Schistosomes resistant to the drug Hycanthone, introduced in the 1960s, were detected within a few years after its widespread use; resistance to another drug, Oxamniquine, also has been reported.

Prophylactic vaccination against schistosomes would be a highly desirable control strategy, provided that genetic variation is not excessive within each schistosome species or that genetically-programmed antigenic modulation (a rapid-response, "anti-immunity" ploy utilized by certain viruses and bacteria, as well as several protozoan parasites, to avoid detection) does not occur in these worms.

One important difference between schistosome infections and infections caused by most viruses or unicellular organisms is that the schistosome worms do not increase in numbers in the mammalian host. Only one worm can be generated per cercaria and one worm of each gender is required for production of eggs. This minimizes the opportunity for schistosomes to utilize the mechanisms which produce antigenic variability in those other infectious agents that undergo replication at high rates.

Within the human host, several different developmental stages of the parasite can be found (Figure 1). Infection is initiated when a person steps in to fresh water and comes in contact with cercariae (Figure 2). After skin penetration, the cercarial heads transform into schistosome larvae (named schistosomula by Al Senft, a name which has been retained) that migrate, differentiate, and grow, eventually becoming adult male or female worms. These adults pair and produce hundreds of eggs per day, most of which pass into the environment. Upon contact with fresh water, the eggs hatch and release the motile miracidia, which infect the appropriate snail intermediate host.

It is hoped that a multivalent vaccine can be produced which will stimulate strong immune responses to several different target antigens, increasing the immune attack rate, thereby overwhelming parasite escape mechanisms.

Thus, within an infected individual, at least three distinct stages can be found (schistosomula, worms, and eggs), each with unique as well as shared antigens. As a result, one must continue to be aware of the possibility that different stages of the schistosome life cycle might express different antigenic determinants; ie, parasites may developmentally regulate expression of potential target antigens. Moreover, selective pressure occurring during evolution of the host-parasite relationship have probably influenced the "potency" of the parasite antigens, resulting in partial immunity. Another concern, in choosing the antigenic components for a vaccine, is the capacity of schistosomes to escape destruction by utilizing processes which inactivate the effector phase components of the immune system, eg, by binding antibodies or complement component C1q in non-functional conformations to Fc- or C1-receptor "mimics" on the worm surface and then destroying them by proteolysis. It is hoped that a multivalent vaccine can be produced which will stimulate strong immune responses to several different target antigens, increasing the immune attack rate, thereby overwhelming parasite escape mechanisms. This strategy would also address the concerns over developmentally regulated target antigens. Finally, since certain antigens of the worm cross-react with components of the parasite's egg, there is a danger of inducing a state of immunological hypersensitivity against the egg. This is a potential risk factor of immunization, especially if the vaccine is only partially successful in preventing the larval stages of the parasite in attaining maturity to egg-producing adults (a more likely result, in light of the concerns over potency of parasite antigens and of escape mechanisms mentioned above). Even with fewer worm pairs, a hyperimmune response to the eggs may result in more severe pathological consequences relative to those occurring in nonvaccinated hosts with higher worm burdens. Immunomodulatory strategies are being explored as a way to minimize this consequence or to treat those infected individuals with a genetic predisposition to develop hypersensitivity to eggs. Thus, the choice of a vaccination strategy will be influenced by considerations requiring detailed knowledge of the host-parasite interaction.

Protective Immune Responses to Schistosome Infections

Laboratory Models

Several animal models have been utilized to demonstrate that previously infected hosts develop "resistance to reinfection", the necessary (but not sufficient) criterion which is usually applied to establish the existence of specific protective immunity in infectious diseases. This resistance is assessed either by measuring yields of worms derived from cercariae of the secondary (also called challenge) infection or by assessing the consequences of the secondary infection on egg output. The resistance is usually partial *but significant*, resulting in 60-80% reductions in expected challenge worm yields. The partial protection is possibly due to features of the schistosomes mentioned above (reduced antigen potency; escape mechanisms to avoid immune detection). One convenience in studying schistosomiasis is that each parasite species has

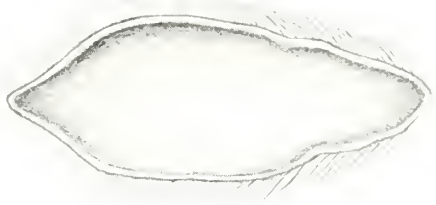
Figure 1

GROWTH STAGES OF SCHISTOSOMA MANSONI

OVUM

115-180μ

MIRACIDIUM



CERCARIAE

SCHISTOSOMULUM

ADULT MALE and
FEMALE WORMS

ADULT MALE 1 CM
ADULT FEMALE 1.6 CM

©MARY ELIZABETH GORDON

a wide range of mammalian species which can serve as hosts for completion of the sexual phase of the life cycle (permissive hosts). In addition, certain nonpermissive hosts (susceptible to cercarial infection, but unable to support completion of the entire mammalian phase of the parasitic life cycle) have also yielded significant information on the development of protective immunity to the parasite. Initially, the rhesus monkey (permissive host) was the first model in which resistance to reinfection was demonstrated (Smithers & Terry, 1969). Unfortunately, however, efforts to transfer a protective activity using the serum of chronically-infected, resistant monkeys to naive rhesus monkeys were unsuccessful. The capacity to demonstrate that protection is due to specific antibodies in the serum or lymphoid cells from a resistant host is one of the criteria which could be used to support the conclusion that resistance to reinfection is due to stimulation of the immune system. This demonstration is not only theoretically important, but also provides an entry into the more difficult task of identifying which of the myriad of schistosome antigens are candidates for inclusion in a vaccine which would induce the protective immune response.

A second chronic-infection model of resistance utilized laboratory mice (permissive host), in which resistance to infection was easily induced by exposure to very few cercariae. Again, however, efforts to transfer resistance with immune mouse serum yielded erratic results. Ultimately, Dean (1981) introduced a parabiotic mouse model in an effort to determine if the resistance could be transferred by the blood (by antibody and/or by lymphocytes) from the infected mouse to the noninfected partner. Pairs of genetically identical mice were surgically connected to share the same blood supply, one mouse normal and one already chronically infected. In this model resistance in a chronically infected mouse could not be transferred to a naive partner exposed to cercariae after establishment of parabiosis. Subsequently, it was found that portal-caval shunting (a major consequence of the pathology in chronically infected mice) probably accounts for failure of worms from the second infection to become established in the portal circulation. Resistance to reinfection in such models was re-interpreted as an epiphenomenon, in which migrating larval worms from the second infection were unable to establish residence in the portal sinusoids (a process required for maturation of larvae into adults), and instead were shunted back to the lungs. The larvae can become trapped in the lungs (a natural but high-risk, intermediate station in the migratory pathway), and ultimately be expelled into the alveolar air spaces, where an aggressive monocytic cell attack leads to their death (Wilson, 1990).

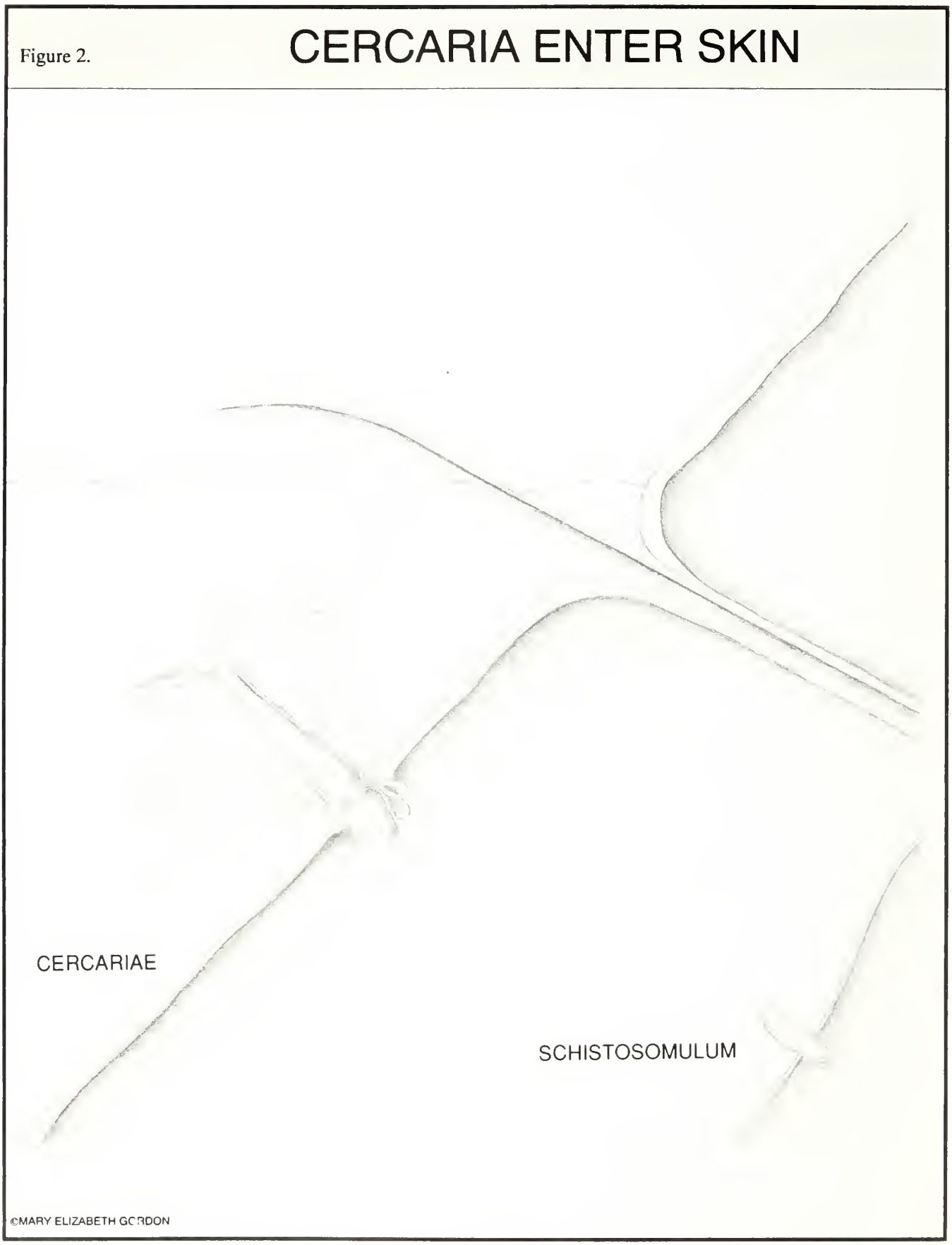
Much information relevant to vaccine development has been derived using mouse models in which chronic infections are avoided, by infection with radiation-attenuated cercariae (resultant larval parasites are arrested in the lung during first passage). Similarly, infection of laboratory rats, a nonpermissive host, with normal cercariae has also been useful. In the rat, the life cycle is essentially aborted at the stage when paired adult worms migrate from the portal sinusoids to the mesenteric veins (Cioli, Knopf & Senft, 1977). In both models, there is again partial resistance to reinfection, but *more importantly*, protective activity can be effectively transferred using serum from twice-exposed hosts. Antibodies in these protective immune sera have been used to identify candidate vaccine antigens, as will be described below.

The evidence that there is resistance to reinfection resulting from exposure either to irradiated cercariae (in permissive or nonpermissive hosts) or to normal cercariae in nonpermissive hosts is quite convincing. In addition to demonstrating that protective activity resides in the immunoglobulin fraction of serum, it is also possible to show that resistance to a challenge infection is conferred to the naive partner of a mouse infected with radiation-attenuated cercariae in the parabiotic mouse model. Moreover, using radiolabelled cercariae for the challenge infection, their migration can be monitored. In both mice and rats, as well as in guinea pigs, another nonpermissive host, this tracking assay identifies the lungs as the major site of trapping of challenge infection larvae, but evidence of trapping in the skin or post-lung migratory stage have also been reported. Involvement in larval parasite elimination of specific antibodies together with leukocytes (which bind to the Fc region of the antibodies) is referred to as Antibody-Dependent Cellular Cytotoxicity (ADCC). In all cases, larval parasites are eliminated before maturation to egg-laying worm pairs.

A second approach to avoiding the problems associated with pathology has been to vaccinate with parasite extracts, ie a "nonliving vaccine" model. Successes with these nonliving parasite vaccines provide optimism that "subunit" vaccines are possible using isolated components of the parasite, as has been successfully demonstrated for certain viral and bacterial vaccines. The subunit vaccine approach will be expanded upon below. The nonliving vaccine in mice induces strong delayed-type hypersensitivity reactions which may trap migrating larval parasites more effectively in the lungs (James and Sher, 1990). In rats, the nonliving vaccine stimulates humoral immunity, similar to live cercarial infections, and the antibodies also act to trap larvae in the lungs.

In addition to these conventional approaches, the modern strategy of producing protective monoclonal antibodies has likewise yielded promising candidate vaccine antigens. Monoclonal antibodies (MoAbs) are homogeneous immunoglobulins having specific antigen-binding properties, secreted by *in vitro* cultured cell lines known as hybridomas. Construction of hybridomas requires rodent myeloma cells (or mouse/human hybrid cell lines) which can be maintained indefinitely in culture medium, but which have lost their capacity to produce immunoglobulin (possibly through chromosomal rearrangement).

Figure 2.


CERCARIA ENTER SKIN
CERCARIAE
SCHISTOSOMULUM
©MARY ELIZABETH GORDON

Mixing suspension of activate lymphoid cells from immune or reinfected rodents with the myeloma cells (or peripheral blood leukocytes from infected humans) with the transformed cells, under conditions which promote cells to fuse their plasma membranes, results in "hybrid" cells that combine the antibody-producing potential of the normal cells with the immortality of the tumor or transformed partner, hence the name hybridoma. Performing these fusions under appropriate conditions and subjecting the fused cells to selective conditions favoring the growth of the hybrid cells, it is possible to generate a wide variety of such cells. Finally, screening strategies can be devised which permit selection of individual hybridomas, on the basis of the antigen-binding specificity of the antibody they secrete. This antibody is encoded by chromosomal DNA acquired from a single, normal lymphoid cell and is therefore homogeneous, with a high probability of being unique with respect to the precise epitope to which it can bind (if its binding affinity is also considered). Each individual hybridoma can be grown to a high cell density, conceivably forever in culture, from a single cell. Hence a cloned hybridoma cell line can be generated from each antibody specificity isolated.

The major challenge facing someone interested in producing hybridomas which are "protective" against the disease, hence capable of identifying target antigens of the parasite, is the screening strategy. What parasite target should be used to identify antibodies in hybridoma culture supernatant fluids? (Production of hybridomas producing monoclonal antibodies capable of recognizing predefined antigens is a much simpler task, and has been successful, eg, 97 kDa paramyosin, Pearce et al, 1988.) In the case of schistosomes, there were two assumptions applied to the choice of mass screening strategy. These assumptions were: 1) the target Ags would be on the surface tegument of the parasite and 2) the target Ags would be expressed by the earliest stage of the parasite life cycle, ie, the skin schistosomula, or more precisely the *in vitro* equivalent of this stage generated by any of several methods from cercariae. Furthermore, it was assumed that binding to a single epitope would be sufficient to engage the host mechanism involved in recognition of Ag:Ab complexes leading to parasite elimination (ie, ADCC). While protective monoclonal Abs have indeed been detected through screening utilizing the schistosomula, it is now accepted that authentic skin stage larvae resulting from a natural infection are *not* killed in the skin, but instead die in the lungs (as mentioned above). This surprising result could be explained by postulating that protective immune effector mechanisms are inefficient while the larvae are in the skin, in spite of their expression appropriate target Ags. An exception to this is a monoclonal selected using eggs can block migration in the skin (Harn et al, 1984).

Protective immune sera or MoAbs are each used to identify candidate vaccine antigens. If these antigens are proteins, then there are techniques available for synthesizing such products (see below). Some target epitopes of protective antibodies, however, are the polysaccharide portion of a glycoprotein. Methods for chemically or biochemically synthesizing polysaccharides are not as advanced as those available for synthesizing protein antigens. At present, another technique is being explored for synthesizing molecules capable of inducing anti-polysaccharide antibodies. This technique involves producing a different population of antibodies, which react with the hypervariable region of the protective anti-polysaccharide MoAbs. These anti-(MoAb variable region) antibodies are called anti-(idiotypic), or just anti-Id, antibodies. A subset of these anti-Id antibodies can be shown to possess a 3-dimensional structure which "mimics" the polysaccharide epitope (ie, it is an "antigen image"); such structures can be called "mimotopes" (although the concept of mimotopes now extends beyond anti-Id antibodies to any structure that mimics an antigen). The mimotope can be synthesized in large quantities, since it is a protein, and used as the vaccine. This approach has already been used successfully in *S. mansoni* using two different carbohydrate vaccine molecules. However, their usage is predicated upon the assumption that it will be possible to stimulate immunological memory in both B and T lymphocytes which can be recalled by the natural infection.

As described above, some vaccination protocols identify antibody-*independent* cell-mediated immune reaction as the effector phase of the protective immune response. In the case of schistosomes, these cell-mediated reactions involve CD4+ T cells and macrophages. Cytokines secreted by the T cells activate the macrophages, which then appear to secrete other cytokines that are toxic to the larval parasites. Other parasites (usually viruses) are eliminated by cytolytic T cells, which can be CD4+ or CD8+. In order to induce these T cell protective immune responses, the form of the vaccine is again important. The requirement of inducing the appropriate immune response(s), ie, humoral or cellular, are described below.

In summary, information from studying immunity in a variety of animal models and application of modern technologies have led to the identification of candidate vaccine antigens. The issue arises as to the relevance of these antigens to humans. For example, does the human immune system recognize these antigens and is the effector phase of the human immune response appropriate for parasite elimination? Is there evidence for protective immunity in humans? Humans cured of schistosome infections and then monitored over several subsequent months (to document re-exposure to cercariae) fall into two categories: 1) return to positive egg output at either previous or lower levels or 2) no longer egg positive. The latter group have been defined as resistant to reinfection and their immune status is being compared to the group which retains susceptibility. These findings are still subject to the question: does resistance equal immunity? (ie, are we observing

portal-caval shunting?, as described above in the chronic mouse model.) Capron & Butterworth (Butterworth, 1990) believe that protective antibodies are present in the sera of resistant persons, and that "blocking" antibodies are present in the sera of nonresistant persons, the latter interfering with the effector activity of the former (isotype-specific or epitope-specific?). A resolution of these issues requires further study.

Candidate Vaccine Antigen Identification: *Production of Antigens Using Recombinant DNA Technology*

If the candidate vaccine antigen is a protein, then the messenger RNA (mRNA) encoding this protein is present in the stage(s) of parasite producing this protein. The capacity to "clone" this mRNA directly is the technological breakthrough which has led to the ability to synthesize the encoded protein antigen in large quantities. To identify the desired mRNA, one first converts an RNA extract to the parasite into complementary DNA (cDNA) sequences using the enzyme Reverse Transcriptase. One then constructs a "cDNA library" (by inserting the cDNA products into a suitable vector using recombinant DNA techniques) and expands each chimeric vector clonally by introducing them into suitable host cells. If the chimeric vector is engineered to express the cDNA, ie, transcribe and translate, it is possible to screen a large number of clones with protective MoAbs or, as our lab has developed (El-Sherbeini, et al 1989) by using a contrasting antiserum assay (screening first with antibodies in a protective infection or vaccine polyclonal antiserum and then excluding reactive clones which also bind to antibodies in nonprotective antisera). There are several pitfalls in this approach (incomplete cDNA; lack of expression of antigenic product; etc.), but it has been successful for schistosome antigen identification. One may also screen by using synthetic RNA sequences based upon knowing the amino acid sequence of the candidate antigen, which does not require expression for the protein. However, since the codons specifying amino acids are redundant, many synthetic sequences must be generated. Once a cDNA clone has been identified and its nucleotide sequence determined, one can then search for a full-length cDNA clone or screen a genomic library using the cDNA sequence as a pair. To confirm isolation of the desired antigen, one may use the recombinant product to immunize a normal host and determine if the antibodies produced react with the expected, authentic parasite protein. Expression of the full-length protein in microbial system (bacteria or yeast) or in mammalian cell line is then pursued. The latter system affords the opportunity to synthesize glycoproteins, an especially important consideration if the polysaccharide is the critical epitope for immune effector recognition. This approach is an alternative to the anti-Id approach outlined above, and yields a product with potentially both B and T cell epitopes. One may then purify the recombinant product and use it as a component of a trial subunit vaccine.

Utilization of Synthetic Peptides as Vaccines

The recombinant DNA technology has already yielded many candidate vaccine antigens (see reviews). Yet, there are efforts to refine this strategy to another level, for a variety of possible reasons. The regions of the vaccine antigens which induce the immunity are called "epitopes" and represent the 3-dimensional arrays of atoms which bind to the antigen recognition molecules (ARMs) on B and T cells. These epitopes are in essence the immunoreactive regions of the vaccine. Identifying and characterizing their properties is becoming a prerequisite for safe and effective vaccines in the minds of some scientists. Knowing the immunogenic potentials of the different epitopes, the following questions can be answered: do they stimulate B or T cell immunity? Which isotypes of Ig are produced? Which type of T cells are activated?.

B cell ARMS are usually recognized epitopes of proteins in their "native" conformation (also called "assembled" conformation, since amino acids from several different parts of the sequence are brought together to form the epitope), while T cell activation requires protein antigen to be processed and presented as short, single peptide fragments (also called "sequential" conformation) in association with the molecules encoded by the genes of the major histocompatibility complex (MHC). Subsets of T cells exist which are reactive to peptides presented in association with class I MHC (CD8+ T cells) or with class II MHC (CD4+ T cells). B cells usually require co-stimulation with both native antigen and with activated CD4+ helper T cells, in order to generate both an antibody response and immunological memory. Subsets of CD4+ T cells are also present, which can stimulate B cells to differentiate along alternative pathways, yielding different classes or subclasses of memory B cells, eg IgG1 or IgG2 or IgE. Since the effector functions of CD4+ or CD8+ T cells, or of the different Ig isotypes, are different, then information on epitopes is essential in order to "direct" the immune response into the desired status, viz. host protective with memory capable of being recalled by a natural infection. Accepting that parasites have evolved their antigens to prevent total elimination by the immune system, it might be possible to "redesign" antigens to overcome this impediment to complete immunity. To that end, it is now possible to construct synthetic peptide antigens, by assembling amino acids into the desired sequence on polymeric backbones, so as to yield a high molecular weight product contain repeat versions of the sequence. Such an "octopus" as it is called (having 8 peptide chains emanating from a single polymeric core) is highly immunogenic when containing both B and T cell epitopes.

Summary

Animal models have provided evidence of the existence of protective immunity. Most systems resistance fall in the range of 40-60%. While an

argument has been made that this level of immunity will already have an impact, and that re-exposure will improve this level of protection, an improvement by reconstructing the antigen would not be ignored. While vaccinated nonresidents visiting endemic areas could be cured of light infection by existing drugs, a protective vaccine appears to be essential for residents of endemic areas since re-infection is now the major problem for control programs.

Adult worms survive while larval worms from a new infection are eliminated by the immune response induced by the resident worms.

Why is there an incomplete immunity to the natural infection? Adult worms survive while larval worms from a new infection are eliminated by the immune response induced by the resident worms. The term "concomitant immunity" is used to describe this observation. Parasites have evolved strategies to minimize the opportunity for host to become reinfected without maximizing elimination of the primary infection parasites. Thus, the "early worm gets the bird" or in the case of schistosomes, the mammal. Increased knowledge on induction of the immune response and on the effector mechanisms operating against schistosomes may lead to a redesign of the antigens, eg, to augment the desired response while avoiding the interfering or blocking immune responses. Several antigens have been identified. Multivalent subunit vaccines have not been tested, but exist as a goal to improve the level of resistance. As stated at the beginning, these rapid advances in our knowledge have emanated from the application of techniques which have permitted cloning of parasite antigens and the extensive new information available on the functioning of the immune system. Even so, the agencies supporting this research endeavor are impatient for success. Hopefully, the goal will be attained by the end of this century, barely 100 years since the seminal work of Pasteur, Koch, Ehrlich, and their colleagues.

Literature Cited

Two excellent books reviewing the current status of vaccine development to schistosomiasis are:

Rollinson G, Simpson AJG, eds. "The Biology of Schistosomes from Genes to Latrines" London: Academic Press, 1987.

Warren K, ed. "The Immunology and Molecular Biology of Parasitic Infections" Third edition. Oxford: Blackwell Scientific Publications, 1992 (in press). Chapter by Newport GR, and Colley DG, "Schistosomiasis".

Butterworth AE. Studies on human schistosomiasis: chemotherapy, immunity and morbidity. Ann Parasitol Hum Comp 65:53-57, Suppl 1, 1990.

Cioli D, Knopf PM, and Senft AW. A study of *Schistosoma mansoni* transferred into permissive and nonpermissive hosts. International Journal of Parasitology 7:293-299, 1977.

Dean DA, Bukowski MA, and Clark SC. Attempts to transfer resistance of *Schistosoma mansoni* infected cercariae-immunized mice by means of parabiosis. American Journal of Tropical Medicine & Hygiene 30:113-120, 1981.

El-Sherbeini M, Bostian KA, and Knopf PM. *Schistosoma mansoni*: Cloning of antigen gene sequences in *Escherichia coli*. Experimental Parasitology 70:72-84, 1990.

Grzych J-M, Velge-Roussel F, and Capron A. "Anti-idiotypic antibodies: An alternative approach to immunoprophylaxis against parasites" in P-A Cazenave, Ed. Progress in Vaccinology, vol. 3. New York: Springer-Verlag, pp. 107-122, 1990.

Harn DA, Mitsuyama M, and David JR. *Schistosoma mansoni*: anti-egg monoclonal antibodies protect against cercarial challenge *in vivo*. Journal of Experimental Medicine 159:1371-1387, 1984.

James SL and Sher A. Cell-mediated immune response to schistosomiasis. Current Topics in Microbiology and Immunology 155:21-31, 1990.

Pearce EJ, and Sher A. Molecular mechanisms of immune evasion in schistosomiasis. Contrib Microbiol Immunol 8:219-232. 1987.

Pearce EJ, James SL, Lanar DE, and Sher A. Induction of protective immunity against *Schistosoma mansoni* by vaccination with schistosome paramyosin. Proceedings of the National Academy of Science 85:5678-5682, 1988.

Smithers SR, and Terry RJ. Immunity in schistosomiasis. Annals NY Academy of Science 160:826-840, 1969.

Wilson RA. Leaky livers, portal shunting and immunity to schistosomes. Parasitology Today 6:354-358, 1990.

Wolowczuk I, Auriault C, Bossus M, Boulanger D, Gras-Masse H, Mazingue C, Pierce RJ, Grezel D, Reid GD, Tartar A, and Capron A. Antigenicity and immunogenicity of a multiple peptidic construction of the *S. mansoni* Sm-28 GST antigen in rat, mouse and monkey. Journal of Immunology 146:1987-1995, 1991.

Acknowledgement

PMK is supported by research grants from the UNDP/World Bank/WHO Special Programme for Research and Training in Tropical Diseases [B20/181/53] and the US Public Health Service, NIH [AI-31224].

The Hemoglobinase of *Schistosoma mansoni*

James H. McKerrow, MD, PhD

As a resident of the portal venous system, the schistosome worm takes advantage of a readily available supply of red blood cells as its major source of protein.

The mark of any successful parasite is its ability to replicate itself at high levels within a host and then successfully transmit infection to new hosts. Schistosome parasites accomplish this in the human host by the production of large numbers of fertile eggs. Depending upon the species, schistosome females may lay hundreds to thousands of eggs per day (Basch, 1991). Considering that the life span of an adult worm may be in excess of ten years, the success of this parasite as a human infection of thousands of years is understandable. In order to produce this high level of progeny, the metabolism of the female (and her male partner) must be remarkably efficient. One of the major contributions that Al Senft made to our understanding of the phatobiology of schistosomiasis was his remarkable insights into many aspects of this parasite's metabolism. A key metabolic pathway for the schistosome is protein metabolism. As a resident of the portal venous system, the schistosome worm takes advantage of a readily available supply of red blood cells as its major source of protein. They ingest and lyse blood cells, releasing the hemoglobin into their gut (Figure 1, Kasschau and Dresden, 1986). Al Senft was instrumental in directing our attention to specific proteolytic enzymes which serve as the key digestive enzymes in hemoglobin metabolism. These proteolytic enzymes have been referred to as "hemoglobinases" (McKerrow and Doenhoff, 1988).

In 1959, Timms and Bueding (Timms and Bueding, 1959) identified a proteolytic enzyme in extracts of *S. mansoni*, with a substrate specificity for hemoglobin, and speculated that this was in fact the enzyme which catalyzed the degradation of host hemoglobin to produce the hematin pigment that accumulates in infected host livers. Throughout the 1960s, Al Senft had been analyzing the biochemical pathways of *S. mansoni* in hope of discovering a new therapy through knowledge of the biochemical properties of adult worms. His attention had been drawn to globin metabolism by the observation of Cheever and Weller (Cheever and Weller, 1958) that the addition of pure globin to an *in vitro* culture media used in maintaining worms doubled the average survival time. Senft also was intrigued by the report of Timms and Bueding of an enzyme that may be key to utilization of globin by the worms. In a pioneering series of papers, Senft and his colleagues at Brown University and at the Marine Biological Laboratory, Woods Hole, defined the properties of this enzyme (Grant and Senft, 1987; Sauer and Senft, 1972). Among their observations was that the end products of globin digestion by the hemoglobinase were small peptides, and that intact globin was a specific substrate as evidenced by the lack of activity against separated α and β globin chains. They managed to partially purify the enzyme seventy-one fold, confirmed an acid pH optimum for the enzyme, and accurately estimated its molecular weight at approximately 27,000. The initial biochemical characterization of this enzyme by Senft and his colleagues encouraged other biochemists to explore protein catabolism in *S. mansoni*. In 1979 Dresden, in collaboration with Deelder (Dresden and Deelder, 1979), demonstrated that the adult worm hemoglobinase was in fact a thiol (cysteine) protease by virtue of its selective inhibition by N-ethyl maleimide and other inhibitors of thiol proteases. Over the next decade, Dresden and his colleagues at Baylor

James McKerrow, MD, PhD, is Associate Professor, Department of Pathology, University of California, San Francisco.

University extended Senft's work in defining the biochemical properties of his enzyme (Bogitsh and Dresden, 1983; Zerda et al, 1988; Dresden, 1982; Dresden et al, 1981). Between 1986 and 1987 the purification of the schistosome hemoglobinase to homogeneity was accomplished by both groups. While on sabbatical in San Francisco, Senft (working in collaboration with another sabbatical visitor in my laboratory, Lindquist from San Francisco State University) successfully purified the major acidic proteinase from adult worms using FPLC (Lindquist et al, 1986). In parallel, Dresden, Chappell, and colleagues purified the enzyme using antibody affinity chromatography (Chappell and Dresden, 1987). Both groups confirmed that the purified enzyme was a cysteine protease with a substrate specificity for peptides containing arginine in the P1 position, ie, the amino acid which is amino terminal to the site of peptide bond cleavage (Berger and Schecter, 1970). It is a sad irony that Senft and Dresden, two pioneers in parasite biochemistry, both died last year. Several other helminth and protozoan parasite cysteine proteases have now been identified with similar substrate specificities to the schistosome hemoglobinase. Proteinases from *Fasciola hepatica* and *Clonorchis sinensis* were also studied by Dresden's laboratory and appear to be homologues of the Schistosoma hemoglobinase (Rege et al, 1989; Song et al, 1990). Genes coding for structurally similar enzymes have been cloned from *Haemonchus contortus* (Pratt et al, 1990) and the free-living nematode *Caenorhabditis elegans* (Ray and McKerrow, 1991). Because of the powerful tools available to analyze *C. elegans* development and gene regulation, the signals that determine how protease biosynthesis is temporally regulated with feeding, and spatially regulated to the parasite intestine, may soon be defined.

The protozoan parasite *Plasmodium falciparum*, the causative agent of falciparum malaria, also has a hemoglobinase which is utilized in the intraerythrocytic stage of malaria infection for hemoglobin degradation (Rosenthal et al, 1989). Likewise, biochemically and structurally similar proteases have been identified in *Entamoeba histolytica* (Bouvier et al, Tannich et al, 1991). *Trypanosoma brucei* (Mottram et al, 1989; Pamer et al, 1990) and *Trypanosoma cruzi* (Eakin et al, 1992). The substrate specificity of these cysteine proteases as well as their structure is remarkably similar to that of the schistosome enzyme. These observations suggest that cysteine proteases may be vital for a number of protozoan parasites and as Senft suggested in the early 1970s, very promising targets for the development of new antiparasitic chemotherapy.

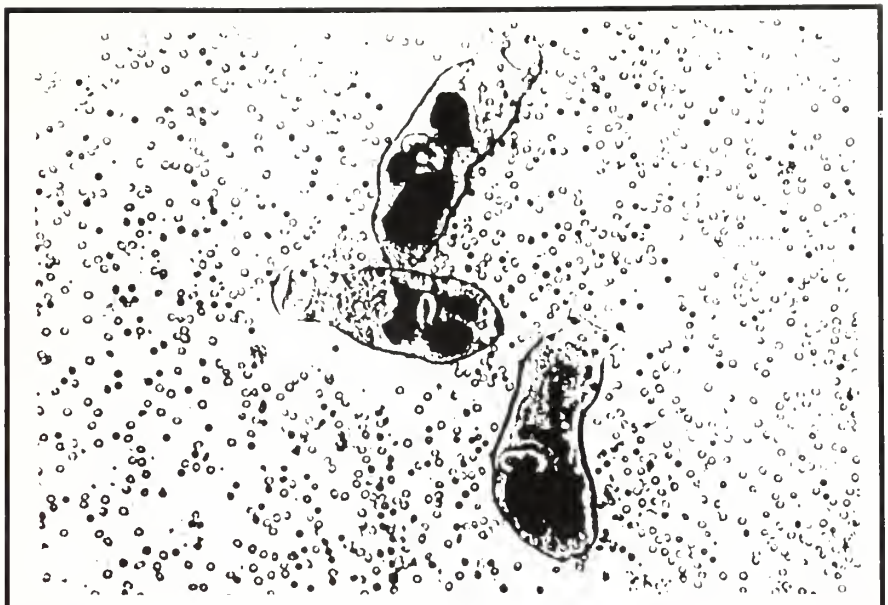


Figure 1. Schistosomula maintained in culture for 28 days. Gut appears dark from digestion of hemoglobin. Compare size with erythrocytes in background. Bright-field microscopy x 100.

The protozoan parasite* Plasmodium falciparum, *the causative agent of falciparum malaria, also has a hemoglobinase which is utilized in the intraerythrocytic stage of malaria infection.

In parallel with his studies of the biochemical properties of the hemoglobinase, Senft and his colleagues made the key observation that this enzyme is very immunogenic in the host. (In fact, the antibody response was so marked that infection could be demonstrated by intradermal skin tests using the partially purified hemoglobinase (Senft et al, 1979). This key observation of the immunogenicity of the cysteine protease of *S. mansoni* has recently been exploited by Chappell and her colleagues as an extremely promising serodiagnostic test for infection by schistosomes (Chappell et al, 1990). As is often the case in scientific research, these observations helped to bring together two parallel lines of study. Deelder and his colleagues in Leiden (Qian and Deelder, 1982) and Ruppel's group at Heidelberg (Ruppel et al, 1985), had both been characterizing the major worm antigens recognized by human sera during schistosome infections. One of these antigens turned out, in fact, to be the cysteine protease of adult schistosomes. Many structurally related cysteine proteases are now recognized as immunogenic, including the major dust mite allergen, the cysteine protease of *E. histolytica* and *T. cruzi*, and papain (McKerrow, 1991).

During the last few years, the isola-

tion of cDNAs coding for *S. mansoni* hemoglobinases has been accomplished. Davis and his colleagues, using an enzyme preparation purified according to the methods of Sauer and Senft (1972), isolated a schistosome cDNA from a schistosome adult λk-gt11 expression library. This cDNA coded for a 31,000 molecular weight protein (Sm31) that was identical to an immunogenic protein previously identified by Deelder and his colleagues (Davis et al, 1987; Qian and Deelder, 1982). Mo-Quen Klinkert independently isolated this clone and a second one called Sm32 (Klinkert et al, 1987; Felleisen et al, 1990). Analysis of the primary sequence of these two clones revealed that Sm32 hemoglobinase had sequence homology to the papain family of cysteine proteases. This homology is consistent with the biochemical properties originally described by Senft and Dresden. The Sm31 hemoglobinase remains somewhat of a mystery in that no sequence homology is apparent to any eukaryotic proteases. However, Chappell and her colleagues have recently suggested this enzyme may be related to cysteine proteases found in certain viruses. In any case, analysis of the sequence of these clones helped to bring together the immunologic work of Deelder and Ruppel and the biochemical work of the Senft and Dresden groups.

. . . the immunogenicity of the cysteine protease of S. mansoni has recently been exploited . . . as an extremely promising serodiagnostic test for infection by schistosomes.

It is a worthwhile lesson for young scientists, as well as experienced ones, to reflect upon the historical development of Senft's ideas about the importance of the hemoglobinase in schistosome digestion. Those of us who knew Al well both as a person and a scientist recognized that he was a true "idea person." It is relatively easy, even in today's world of new biology, to follow a well-trodden research path with logical but pedantic science. It is the rare individual who can lead us in new directions. Whether it was in the area of purine metabolism or protein metabolism in schistosomes, Al Senft raised issues no one had seriously addressed before. Unfortunately, it often takes many years before ideas like this are accepted in the scientific community. Because the field of schistosomiasis research was so long dominated by biochemistry, chemotherapy and metabolism were largely ignored and sometimes viewed disparagingly. The biochemistry of schistosomes, and especially the importance of proteases in parasitic infections, are now recognized as key both in terms of development of new chemotherapy as well as, ironically, in serodiagnosis and vaccine development. Al's original idea that the hemoglobinases of schistosomes may be potential targets for chemotherapy is getting a fresh look. In the last several years, new classes of cysteine protease inhibitors have been developed for *in vivo* (Smith et al, 1988; van Noorden et al, 1988). Ritter, a postdoctoral fellow in my laboratory, has shown that both schistosomula adult worms can be killed in culture with micromolar concentration of fluoromethyl ketone cysteine protease inhibitors (Ritter, unpublished observations). A major research project, undertaken by a consortium of laboratories at the University of California, San Francisco, is exploring the practical application of Al's ideas in the development of lead compounds for use in treatment of many infectious diseases. The successful isolation and expression of cDNA clones for the schistosome hemoglobinases also has opened up the possibility of new and more easily standardized serodiagnostic tests like those being developed by Cynthia Chappell (Chappell et al, 1989; Chappell et al, 1990) and Mo Klinkert (Felleisen et al, 1990). It is a testament to Al Senft's ability to combine his background as a medical practitioner and biochemist that so many of his hypotheses about schistosome infection and its control are being resurrected and confirmed.

References

Basch PF. Schistosomes: Development, Reproduction, and Host Relations. New York: Oxford University Press, p. 248, 1991.

Berger A and Schecter I. Mapping the active site of papain with the aid of peptide substrates and inhibitors. Phil Trans Roy Soc Lond B 256:249-264, 1970.

Bogitsh BJ and Dresden MH. Fluorescent histochemistry of acid proteases in adult *Schistosoma mansoni* and *Schistosoma japonicum*. J Parasitol 69:106-110, 1983.

Bogitsh BJ Kirschner KF. *Schistosoma japonicum*: Ultrastructural localization of a hemoglobinase using mercury labeled pepstatin. Exp Parasitol 62:211-215, 1986.

McKerrow JH, Bouvier J, Sikes A, Reed S, and Keene WE. The cysteine proteinase of *Entamoeba histolytica*: Cloning of the gene and its role as a virulence factor. In Coombs G and North M (eds.) Biochemical Protozoology as a Basis for Drug Design. In Press.

Chappell CL and Dresden MH. Purification of cysteine proteinases from adult *Schistosoma mansoni*. Arch Biochem Biophys 256:460-568, 1987.

Chappell CL, Dresden MH, Gryseels B and Deelder AM. Antibody response to *Schistosoma mansoni* adult worm cysteine proteinases in infected individuals. Am J Trop Med Hyg 42:335-341, 1990.

Chappell CL, Hackel J and Davis AH. Cloned *Schistosoma mansoni* proteinase (hemoglobinase) as a putative serodiagnostic reagent. J Clin Microbiol 27:196-198, 1989.

Cheever AW and Weller TH. Observations on the growth and nutritional requirements of *Schistosoma mansoni in vitro*. Am J Hyg 68:322-339, 1958.

Davis AH, Nanduri J and Watson DC. Cloning and gene expression of *Schistosoma mansoni* protease. J Biol Chem 262:12851-12855, 1987.

Dresden MH. Proteolytic enzymes of *Schistosoma mansoni*. Acta Leidensia 498:81-99, 1982.

Dresden MH and Deelder AM. *Schistosoma mansoni*: Thiol proteinase properties of adult worm hemoglobinase. Exp Parasitol 48:190-197, 1979.

Dresden MH, Rutlege ML and Chappell CL. Properties of the acidic thiol proteinase from *Schistosoma mansoni* adults. Molec Biochem Parasitol 4:61-66, 1981.

Eakin AE, Mills AA, Harth G, McKerrow JH and Craik CS. The sequence, organization and expression of the major cysteine protease (cruzain) from *Trypanosoma cruzi*. J Biol Chem, in press.

Felleisen R, Beck E, Usmany M, Vlak J and Klinkert M-Q. Cloning and expression of *Schistosoma mansoni* protein Sm32 in a baculovirus vector. Mol Biochem Parasitol 43:289-292, 1990.

Felleisen R, Klinkert M-Q and Beck E. *Schistosoma mansoni*: Localization of antigenic regions on the 31 kilodalton diagnostic protein. Molec Biochem Parasitol 30:19-26, 1988.

Grant CT and Senft AW. Schistosome proteolytic enzyme. Comp Biochem Physiol 388:663-678, 1971.

Kasschau MR and Dresden MH. *Schistosoma mansoni*: Characterization of hemolytic activity from adult worms. Exper Parasitol 61:201-209, 1986.

Lindquist RN, Senft AW, Petit M, and McKerrow JH. *S. mansoni*: Purification and characterization of the major proteinase from adult worms. Exp Parasitol 61:398-404, 1986.

McKerrow JH. New insights into the structure of *Trypanosoma cruzi* protease. Parasitol Today 7:132-133, 1991.

McKerrow JH and Doenhoff MJ. Schistosome Proteases. Parasitol Today 4:334-340, 1988.

Mottram JC, North MJ, Barry JD and Coombs GH. A cysteine proteinase cDNA from *Trypanosoma brucei* predicts an enzyme with an unusual C-terminal extension. FEBS Letters 258:211-215, 1989.

Pamer EG, Davis CE, Eakin A and So M. Cloning and sequencing of the cysteine protease cDNA from *Trypanosoma brucei rhodesiense*. Nucleic Acids Res 18:6141, 1990.

Pratt D, Cox GN, Milhausen MJ and Boisvenue RJ. A developmentally regulated cysteine protease gene family in *Haemonchus contortus*. Molec Biochem Parasitol 43:181-92, 1990.

Qian ZL and Deelder AM. Circulating antigens in *Schistosoma*-infections. Acta Leidensia 49:71-80, 1982.

Ray C and McKerrow JH. Gut-specific and developmental expression of a *Caenorhabditis elegans* cysteine protease gene. Mol Biochem Parasitol, in press.

Rege AA, Herrera PR, Lopez M and Dresden MH. Isolation and characterization of a cysteine proteinase from *Fasciola hepatica* adult worms. Mol Biochem Parasitol 35:89-96, 1989.

Rosenthal PJ, McKerrow JH, Aikawa M. Nagasawa H and Leech JH. A malarial cysteine proteinase is necessary of hemoglobin degradation by *Plasmodium falciparum*. J Clin Invest 82:1560-1566, 1988.

Rupel A, Diesfeld JH and Rother U. Immunoblot analysis of *Schistosoma mansoni* antigens with sera of schistosomiasis patients: Diagnostic potential of an adult schistosome polypeptide. Clin exp Immunol 62:449-506, 19085.

Sauer MCV and Senft AW. Properties of a proteolytic enzyme form *Schistosoma mansoni*. Comp Biochem Physiol 42B:205-220, 1972.

Senft AW, Goldberg MW and Byram JE. Hemoglobinolytic activity of serum in mice infected with *schistosoma mansoni*. Am J Trop Med Hyg 30:96-101, 19891.

Senft AW, Weltman JK, Goldgraber MB, Egyud LG and Kuntz RE. Species specificity of the immediate hypersensitivity to schistosomal proteolytic enzyme. Parasite Immunol 1:79-89, 1979.

Smith RE, Rasnick D, Burdick CO, Cho K, Rose JC and Vahratian A. Visualization of time-dependent inactivation of human tumor cathepsin B isozymes by a peptidyl fluoromethyl ketone using a fluorescent print technique. Anticancer Res 8:525-530, 1988.

Song CY, Dresden MH and Rege AA. *Clonorchis sinensis*: Purification and characterization of a cysteine proteinase from adult worms. Comp Biochem Physiol 97B:825-829, 1990.

Tannich E, Scholze H, Nickel R, and Horstmann RD. Homologous cysteine proteases of pathogenic and nonpathogenic *Entamoeba histolytica*. J Biol Chem 266:4798-4803, 1991.

Timms AR, Bueding E. Studies of a proteolytic enzyme from *Schistosoma mansoni*. Brit J Pharmacol 14:68-73, 1959.

van Noorden CJF, Smith RE and Rasnick D. Cysteine proteinase activity in arthritic rat knee joints and the effects of a selective systemic inhibitor, Z-Phe-AlaCH2F. J Rheumatol 15:1525-1535, 1988.

Zerda KS, Dresden MH and Chappell CL. *Schistosoma mansoni*: Expression and role of cysteine proteinases in developing schistosomula. Exp Parasitol 67:238-246, 1988.

RHODE ISLAND COMPUTERIZED IMAGING, INC.

Cat Scan Facility
401•751•1110

weekdays
7 am - 5 pm

- Evening appointments for contrast studies
- Medicare, Ocean State
  Rhode Island Blue Cross/Blue Shield approved
- Board Certified Radiologist

Located in: Atwood Medical Center
Suite LL3
1524 Atwood Avenue
Johnston, RI 02919

Chemotherapy of Schistosomiasis

Mahmoud H. el Kouni, BSc (Hon), MSc, MA, PhD

. . . because of a large immigrant population from endemic areas, physicians in California, New York and Florida are increasingly being called upon to diagnose and treat schistosomiasis.

Introduction

Schistosomiasis is a parasitic disease with a wide range of clinical manifestations. The disease affects more than 200 million people in 73 countries and it results from infection with any of three species (*Schistosoma japonicum, S. mansoni*, and *S. haematobium*) of the trematode Schistosoma. Debate still prevails as to whether *S. mekongi* is a separate disease-causing schistosome or a variant of *S. japonicum*.

At the present time most endemic rural populations will have a 40% to 60% prevalence rate at any one time; but almost everyone (95%), has had an infection sometime during his life. These estimates, superimposed on the 1.5 billion humans in schistosome endemic areas, easily qualify schistosomiasis as one of the major world public health problems. Owing to the absence of an appropriate snail population and the presence of more sophisticated sanitation systems, schistosomiasis is not transmitted in North America and Europe. However, because of a large immigrant population from endemic areas, physicians in California, New York and Florida are increasingly being called upon to diagnose and treat schistosomiasis.

The clinical disease dates as early as 1500 BC. Calcified Schistosoma eggs have been identified in Egyptian mummy tissues from the twentieth dynasty (1200 to 1090 BC). In China, there are records of schistosomiasis of comparable antiquity. Schistosoma infections in the New World are more recent in origin, probably beginning with African slave trade to the Americas during the sixteenth and seventeenth centuries.

In 1851, Theodore Bilharz, whose name became synonymous with the clinical human disease (bilharziasis), identified the worm *S. haematoboium* as the causative agent of Egyptian endemic hematuria. The differentiation of the three major disease-causing species was not noted until the early twentieth century by Sir Patrick Manson. The first effective chemotherapy, tartar emetic, was introduced by McDonough in 1918.

Pathogenesis and Pathology

The pathogenesis and pathology of schistosomiasis are largely ones of host reaction to a foreign body, the different stages of the schistosome parasite. Upon infection, mild transient foreign body reactions are seen. However, the most predominant pathology results from the granulomatous response to the unending accumulation of schistosome eggs (each female lays hundreds of eggs every day) which eventually leads, among other symptoms, to liver failure, hepatofibrosis, portal hypertension with the shifting of hepatic blood flow from mainly portal to arterial sources and bladder carcinoma in chronic urinary tract schistosomiasis.

Treatment of Schistosomiasis

Schistosomes are not effectively attacked by circulating host immune antibodies, and they are also not easily killed by cellular components of defense, such as polymorphonuclear cells, eosinophils, macrophages, or immunosecretory cells. In fact, schistosomes appear to be able to coat themselves with host antigens in such a way that they are not recognized as foreign bodies by the host immunosurveillance system.

Since antischistosomal vaccines are not yet available (see article by Knopford and Sun), chemotherapy still is the mainstay to control this disease.

Mahmoud H. el Kouni, BSc (Hon), MSc, MA, PhD, is Associate Professor, Department of Pharmacology, University of Alabama at Birmingham, Birmingham, Alabama.

Until very recently treatment of schistosomiasis was highly unsatisfactory. Over the past few years, there has been a marked improvement in the management of patients with schistosomiasis. New nontoxic and efficacious drugs are now available.

Targets for Chemotherapy

Most available antischistosomal drugs have been discovered by screening of many compounds for efficacy against parasites in animal models. Few of these drugs have been traditionally designed. This is largely because, until very recently, little was known about the basic biochemistry, physiology, and molecular biology of schistosomes and of their interactions with their hosts. The following are some of the potential targets in the biochemistry, metabolism and physiology of schistosomes which have been manipulated to treat schistosomiasis.

Interference with the Coordination of Neuromuscular Activity. The long term survival of schistosomes in the host depends on their ability to maintain their position within the chosen veins. This requires coordinated neuromuscular activity since any agent that interferes with neuronal signaling and/or excitation-contraction coupling in the parasite may have antischistosomal activity. This could be achieved by at least two ways; a) In schistosomes the movement of muscles (chiefly those of suckers, somatic longitudinal and circular muscles, gut peristalsis) is mediated by an acetylcholine/serotonin system. Acetylcholine induces flaccidity or non-movement while serotonin stimulates rapid contraction or movement. Selective inhibition of the parasite acetylcholinesterase would lead to paralysis of the worm. b) Because of the low resistance pathway between the tegument and muscle fibers, disturbing the ionic conductance at the parasite's surface will affect the underlying muscle directly.

Interference with Carbohydrate Metabolism and Glycogen Storage/ Recovery Systems. In contrast to the mammalian host which derives its energy from aerobic metabolism, adult schistosomes by virtue of an incomplete citric acid cycle, are nearly totally dependent on anaerobic glycolysis for their energy requirement. The adult schistosome utilizes one fifth of its dry body weight of glucose per hour, converting 80% to lactic acid. Schistosomes also accumulate carbohydrates in the form of aggregations of glycogen of various molecular weights. Thus, polymers of glucose can be found within several storage sites, for instance within tegumentary nodules on the surface of *S. mansoni* (but not on *S. haematobium* or *S. japonicum*). Another location of glycogen depositions is within the musculature of worms. It is not clear why the worms store glycogen, since they live in a blood environment in which constant glucose levels are maintained. It is postulated that glycogen may be the obligatory source for energy production in some tissues of the worm. Glycogen may also be required for maintaining the functional and/or structural integrity of the parasite. Hence, when worms become glycogen-depleted they die. Therefore, the glycolytic pathway represents another potentially good target for chemotherapy.

. . . schistosomes appear to be able to coat themselves with host antigens in such a way that they are not recognized as foreign bodies by the host immuno-surveillance system.

Interference with other Metabolic Pathways. Other metabolic differences between the parasite and their host, such as the absence of *de novo* pathways for the synthesis of purine or steroids, differences in nucleoside transport and properties of enzymes of pyrimidine metabolism represent additional sites for selective chemotherapeutic intervention.

Antischistosomal Drugs

We will illustrate how several of the past and current antischistosomal agents attempt to manipulate such targets for effective treatment of schistosomiasis. We will also give an example of how differences between schistosomes and their host can be used to rationally design a highly selective chemotherapeutic regimen for the treatment of the disease.

Praziquantel (Biltricide). This is the newest and most effective drug for treating schistosomiasis. It is effective orally in a single dose against all species of schistosomes infecting man with 70% to 95% cure rates. Side effects (eg, nausea, abdominal pain, and vomiting), usually are of short duration, beginning a few hours after treatment, and disappearing spontaneously within 48 hours. It is not a perfect drug since at the higher doses used to treat *S. japonicum* split doses must be used and because of no prior testing in these groups, it is not recommended for pregnant or lactating women.

Praziquantel is a mixture of stereoisomers of pyrazinoisoquinoline ring structures. It is quite lipophilic and rapidly taken up and concentrated (3.5-fold) by the worm. No preferential localization or metabolism by the worms have been detected. The mode of action of praziquantel is unknown. Most evidence implicates the susceptibility of muscle and tegmental systems as important sites of action. Praziquantel effect on the worms is very dramatic. Worms exposed to 1 uM praziquantel *in vitro* show almost an instantaneous and sustained contraction with a half-maximal effect time of 12 sec. This contraction results in paralysis of the parasite leading to the hepatic shift observed *in vivo* which is 95% complete within 5 min after a single oral dose in infected mice. The muscle contraction and paralysis are not due to direct effect on the nervous system since it is not prevented by carbachol, serotonin, dopamine or other agent acting on putative receptor sites.

The effect of praziquantel on worm muscle tension seems to result from the ability of the drug to increase the permeability of the worm muscle cells to calcium ions. Although praziquantel

does not possess the properties of an ionophore its onotropic effects are partially mimicked by the Ca^{++} ionophore A-23187. However, the Ca^{++}-dependent effect of praziquantel appears not to be mediated by specific membrane Ca^{++} channels, since neither voltage dependent (eg, nifedipine) nor voltage independent (amrinone) Ca^{++} channel blockers antagonize the response.

Praziquantel also causes severe destruction of the worm's tegument. Ca^{++} is also implicated in this effect. It is postulated that the drug, by mobilizing Ca^{++}, severely destabilizes the worm surface, rendering it susceptible to the host humoral immune defense. However, tegumental disruption by itself seems not to be lethal to the parasite. Subcurative doses of praziquantel have been shown to cause such lesions *in vivo* and were tolerated by the worms. Furthermore, various compounds that do not have antischistosomal activity were shown to induce similar tegument disruption, and removal of the worm tegument by Triton X-100 did not affect the contractility of the parasite muscle.

The effect of praziquantel on worm muscle tension seems to result from the ability of the drug to increase the permeability of the worm muscle cells to calcium ions.

The most recent studies suggest that parasitologic cure with Praziquantel requires an intact host B-cell immune system. Animals who are made B-cell deficient at birth and then infected with schistosomes cannot be cured with Praziquantel, even at very high doses. If, however, these animals are given serum from normal animals with schistosomiasis they can be easily cured. This has led to the theory that this drug works in concert with the immune system by exposing key surface antigens (disruption of Teguel) or interfering with antigen masking.

This concept appears to hold up in man. Individuals who cannot be cured of schistosomiasis even with repeated doses of Praziquantel and even with more than adequate blood levels have had parasite eggs collected from their stools, passed through snails and used to infect mice. These animals show no differences in cure rates with Praziquantel than normal suggesting that the original lack of cure was more a problem with the host than the worm. As a result no one has definitely demonstrated the development of Praziquantel resistance in this helminth.

Metrifonate is active against both *S. haematobium* and *S. mansoni in vitro* but only against *S. haematobium in vivo*. This can be explained by the fact that when *S. haematobium* is paralyzed by metrifonate, worms are swept back to the lungs where they are trapped and die. In contrast, paralyzed *S. mansoni* are shifted back to the liver and although the liver is not a hospitable site some worms survive and remigrate back to the mesenteric veins where they resume egg laying. Clinical tolerance to this drug is very good. Nausea, vomiting, and bronchospasm have been reported but are rare.

Hycanthone (Etrenil). Hycanthone has been used for mass chemotherapy because it can be administered by a single intramuscular injection of 2.5 mg/kg. The drug is quite effective against *S. mansoni* and *S. haematobium*, but is not very helpful against *S. japonicum*. Cure rates for *S. mansoni* and *S. haematobium* infections approach 95%; however, side effects of vomiting and diarrhea are common. Occasional severe liver damage in humans and mutagenesis and carcinogenesis in animal model experiments have reduced the use of hycanthone.

Hycanthone is thought to bind to acetylcholine receptor sites, especially in the anterior ganglionic network of susceptible worms. This causes an increased uptake of serotonin and leads to overstimulation of the worms. Hycanthone also inhibits, somewhat, schistosomal acetylcholinesterase, but it has less effect on the isoenzyme in mammals. Furthermore, hycanthone-treated worms can be shown to have surface damage some days after exposure.

Hycanthone is also reported to inhibit the incorporation of uridine into nucleic acids in sensitive but not hycanthone-resistant worms. As a result of these changes, worms may lose the capacity to feed properly. Their ceca will become emptied of pigment, and the vitelline gland, drawing its principal nutrition from products of hemoglobin digestion, will degenerate. The worms will appear to starve to death. Intercalatation of hycanthone with DNA may be the basis of the mutagenicity which have been reported in bacteria (but not in animals or humans given this drug).

Antimony Compounds. The antimonials were the classical agents used to treat bilharziasis. These drugs were first used by Christopherson in about 1917. The idea of using a heavy metal against the worms was discovered by accident. Christopherson observed that Berber tribesmen in Africa given antimonials against nasocutaneous Leishmaniasis soon had less urinary bleeding (a sign of *S. haematobium* infection). Subsequently, a whole new approach for treatment of three species of human helminths based on metal therapy was established with potassium antimony tartrate serving as the prototype of most antimonials used in schistosomal chemotherapy. Antimonials are believed to inactivate phosphofructokinase, a key regulatory enzyme in the Embden-Meyerhof glycolytic pathway. Indeed glycolysis is strongly inhibited by trivalent antimonials. However, selectivity is not great since schistosomal phosphofructokinase is 80-fold more sensitive to inactivation by heavy metal than is the mammalian enzyme. Indeed, antimonial drugs are quite dangerous with a wide spectrum of severe side effects and were phased out as more effective and safer drugs appeared.

Niridazole (Ambilhar). The precise mechanism of action of this nitrothiazole derivative has not been determined. It is postulated that, since niridazole reduced DNA contents in treated worms, this drug, like other

nitroheterocyclics, inhibits DNA synthesis. Most experimental evidence, however, indicates that the antischistosomal activity of this drug comes from glycogen depletion of the adult worm by the induction of accelerated utilization. Glycogen phosphorylase catalyzes the degradation of glycogen in schistosome tissues. This enzyme has two rapidly interconvertible forms: active "a" form and inactive "b" form. Niridazole inhibits the converting enzyme phosphorylase phosphatase, which results in continuous rapid utilization of glycogen. It is postulated that although the drug does not affect the rate of glycolysis in the parasite and that the parasite can presumably meet its energy requirement from the readily available plasma glucose in the host, glycogen could be an essential source for energy production in some tissues of the worm. Glycogen may also be required to preserve the functional and/or structural integrity of the parasite; and when worms become glycogen-depleted, they die. Unfortunately, niridazole also lowers patient muscle glycogen, and muscular weakness is a common side effect. One disadvantage of this drug is that its cure rate in children is only about 70%. Side effects are common and include muscle weakness, anorexia, nausea, vomiting, abdominal pain, and insomnia. One metabolite of niridazole, thiocarbamyl-imidazolidinone, is a potent immunosuppressive drug in man. Another, a 4-keto compound causes transient neurologic disturbances.

In terms of treating schistosomes, niridazole has the advantage of being inexpensive (about $1.00/course) vs the $10-15/course required for other drugs such as oxamniquine or praziquantel. Niridazole is also well-tolerated in children, especially if there is no liver decompensation. Liver failure would favor persistence of the drug and possible neural side effects. One disadvantage is the fact that in children the cure rate is only about 70% after an 8-day course. In adults, the cure rate is higher (about 85%), but almost half of adult patients stop therapy because of the unpleasant side effects.

Oxamniquine (Vansil, Mansil). This tetrahydroquinoline compound is effective against *S. mansoni*, especially the strains in the Americas and West Africa. North and East African strains of *S. mansoni* are less sensitive to this compound where the cure rate for children is only 25%. Side effects are usually mild. Drowsiness and dizziness are the most commonly reported side effects. The site of metabolism and the mechanism of action are unknown. Among the effects attributed to this drug is reduction in the worm ornithine transaminase, ATPase, stimulation of motor activity as well as vacuolization of muscle regions. Recent studies showed that oxamniquine irreversibly inhibits nucleic acids and protein synthesis in adult worms. Males were more susceptible than females to the drug and showed a higher degree of inhibition of protein synthesis.

This drug is about 10-fold more costly than niridazole. Its main advantage lies in the fact that it is an oral drug with limited side effects. The recent increase in drug resistance of the schistosome is of concern in using this medication in mass campaigns and will become an increasing problem in countries like Brazil where this drug is used exclusively.

Oltipraz. This drug has recently been synthesized as an antischistosomal compound and clinically tested. Oltipraz is rather insoluble and is best administered with a meal which is enriched with fats. It is believed that this drug is an inhibitor of glutathione reductase. Worms exposed to oltipraz showed reduction in glutathione levels. Although oltipraz showed promising antischistosomal activity, it was withdrawn because of a phototoxic potential responsible for acute pains at finger tips of 30% of patients after a single dose of the drug and sometimes to photo-onycholysis (losing of finger nails).

Prospects and Recent Experimental Approaches. Rational design of a drug based on biochemical and physiological differences between neoplastic cells and the host has been the goal of many investigators for decades. However, one can cite only limited instances of success of the semi-rational design of drugs for the treatment of neoplasia. On the other hand, because of a greater phylogenic separation, the biology of schistosomes is such that one might expect to have a better chance of discovering exploitable differences between the host and the parasite.

Senft and co-workers . . . established that schistosomes are incapable of de novo purine synthesis and are dependent on their salvage pathway to meet their purine requirements.

One of the most fundamental differences between schistosomes and their mammalian host was the discovery that schistosomes differ significantly from their host with respect to nucleotide metabolism. Senft and coworkers at Brown University established that schistosomes are incapable of *de novo* purine biosynthesis and are dependent on their salvage pathway to meet their purine requirements. Only few mammalian cells resemble the parasite in this respect.

The *de novo* pathway utilizes simple precursors for the synthesis of various purines nucleotides. The salvage pathways, on the other hand, are reutilization routes by which the organism can satisfy its purine requirements from endogenous and exogenous preformed purines. Therefore, these parasites can be selectively deprived of vital purines by blocking or interfering with the parasite purine salvage pathways. One way to intervene with the purine salvage pathways is to use one or more of numerous available purine analogues. However, few purine analogues have been tested as antischistosomal drugs because they were either not efficiently metabolized to the nucleotide level by the parasite or were also very toxic to the host.

An alternative strategy for depriving the schistosomes of purines is to use nucleoside transport inhibitors to block the uptake of purine nucleosides

by the parasite. Recently, however, we reported that, in contrast to mammalian systems, the uptake of purine nucleosides by schistosomes was not inhibited significantly by the nucleoside transport inhibitors, nitrobenzylthioinosine 5'-monophosphate, dilazep, and to a lesser extent by dipyridamole. Therefore, we reasoned that coadministration of a nucleoside transport inhibitor with a toxic purine nucleoside analogue would cause selective toxicity against schistosomes. This indeed was found to be the case when the nucleoside transport inhibitor was coadministered with potentially lethal doses of a urine analogue (tubercidin (7-deazaadenosine) or nebularine) to *Schistosoma mansoni, S. haematobium* or *S. japonicum*-infected mice. We were able to protect the host but not the parasite from the nucleoside analogue toxicity. This mode of host-protection by the use of nucleoside transport inhibitor in combination with a purine nucleoside analogue may provide an attractive alternative for the treatment of schistosomiasis with currently available antiparasitic cytotoxic nucleoside analogues especially in cases where drug resistance is encountered and no satisfactory alternative drugs are available.

In summary, in contrast to previous generations, when essentially the only antischistosomal drugs were the antimonials with their severe side effects, a series of effective agents are now available and more are investigated. Thus, theoretically, all the millions of people afflicted by this disease could be cured. Unfortunately, many of the victims of schistosomiasis cannot afford the cost of medicine. Therefore, schistosomiasis remains a malady to the poor of the developing Third World. Current efforts have focused on the most cost effective use of particularly Praziquantel. Because the patent on this drug will soon expire and a "generic" is already made in South Korea, WHO is attempting to obtain Praziquantel at a greatly reduced cost from Bayer for the future. If they are successful this would dramatically improve the outlook for schistosomiasis control within the next few decades.

Literature Cited

Andrews P. Praziquantel: Mechanisms of Antischistosomal Activity. Pharmac Therapeut 29:129-156, 1986.

Brindley PJ, and Sher A. The chemotherapeutic effect of praziquantel against *Schistosoma mansoni* is dependent on host antibody response. J Immuno 139:215-220, 1987.

Campbell WC, and Rew RS. Chemotherapy of Parasitic diseases, Plenum Press, New York, 1986.

el Kouni MH. Efficacy of Combination Therapy with Tubercidin and Nitrobenzylthioinosine S-Monophosphate Against Chronic and Advanced Stages of Schistosomiasis. Biochem Pharmac 41:815-820, 1991.

el Kouni MH and Cha S. Metabolism of Adenosine Analogues by *Schistosoma mansoni* and the Effect of Nucleoside Transport Inhibitors. Biochem Pharmac 36:1099-1106.

el Kouni MH, Diop D and Cha S. Combination therapy of schistosomiasis by tubercidin and nitrobenzylthioinosine 5'-monophosphate. Proc Natl Acad Sci, USA. 80:6667-6670, 1983.

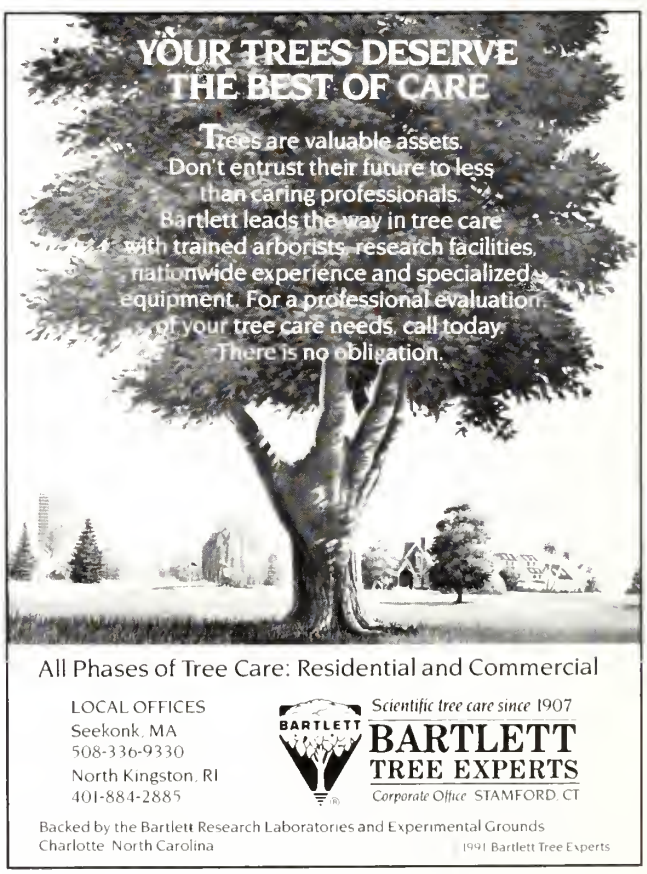
el Kouni MH, Messier NJ, and Cha S. Treatment of Schistosomiasis by Purine nucleoside Analogues in Combination with Nucleoside Transport Inhibitors. Biochem Pharmac 36:3815-3821, 1987.

el Kouni MH and Naguib FNM. Pyrimidine Salvage Pathways in Adult *Schistosoma mansoni*. Int J Parasitol 20:37-44, 1990.

Senft AW and Crabtree GW. Purine metabolism in schistosomes: Potential Targets for chemotherapy. Pharmac Ther 20:341-356, 1983.

This paper was prepared from notes and many discussions the author had with the late Alfred W. Senft, a teacher, colleague and a dear friend to whose memory this paper is dedicated.

Address correspondence to:
Mahmoud H. el Kouni, BSc, MSc, MA, PhD
Department of Pharmacology
University of Alabama at Birmingham
Birmingham, AL 35294


YOUR TREES DESERVE THE BEST OF CARE
Trees are valuable assets. Don't entrust their future to less than caring professionals. Bartlett leads the way in tree care with trained arborists, research facilities, nationwide experience and specialized equipment. For a professional evaluation of your tree care needs, call today. There is no obligation.
All Phases of Tree Care: Residential and Commercial
LOCAL OFFICES
Seekonk, MA
508-336-9330
North Kingston, RI
401-884-2885
BARTLETT
Scientific tree care since 1907
BARTLETT TREE EXPERTS
Corporate Office STAMFORD, CT
Backed by the Bartlett Research Laboratories and Experimental Grounds
Charlotte North Carolina
1991 Bartlett Tree Experts

A Look Ahead in Research and Control of Schistosomiasis

Joseph A. Cook, MD, MPH
Jeffrey W. Mecaskey, MSc

The best bench research is informed by and relevant to the problems of the bedside or the fieldsite where disease control is needed.

The papers in this volume, celebrating the work of the late Dr Alfred Senft, reflect tremendous growth in our understanding of schistosomiasis over the last twenty years. These papers suggest future paths for the research and control of a disease of great importance to the developing world. And yet, though they may indeed predict the future to some extent, it is well to remember that three unforeseen technological developments have altered the recent course of schistosomiasis research: 1) monoclonal antibody production; 2) recombinant DNA technology; and 3) the polymerase chain reaction. Few would have anticipated these changes twenty years ago, and there is some hazard in making predictions of future research today.

In less than two decades, the techniques of biotechnology have revolutionized schistosomiasis research. When Warren and Hoffman prepared their condensation of the selected schistosomiasis literature in 1974, they did not even include a separate section on immunology.[1] In keeping with the chemical and immunochemical techniques of the time, schistosomiasis research centered on the parasitology of schistosomes and their life stages. Papers relating to immunology were placed in sections on diagnosis, pathogenesis, and pathology. In 1992, however, it would be hard to prepare any review of schistosomiasis without a major section on immunological accomplishments.

In recent years, research attention has shifted from the schistosome *per se* to an investigation of the parasite's relation with its host. For example, during the 1950s and 1960s, Senft studied the biochemistry and physiology of the adult worm in an effort to develop anti-schistosomal compounds to control disease.[2] By 1990, however, research in these areas had declined due to the availability of praziquantel and the applications of biotechnology cited above. Following the drug's introduction, interest has waned in understanding the worm's metabolism and rationally designing a drug to interrupt it. At the same time, molecular biology has opened a whole new approach to understanding the schistosome's life cycle through study of genes and gene products.

The introduction of modern biotechnology to schistosomiasis research has helped overcome an old contradiction in parasitic disease control. Traditionally, one thought of sophisticated molecular biology taking place in the industrialized countries, while applied research and control took place where disease was endemic. Fortunately, this is no longer entirely true. The UNDP/World Bank/WHO Special Programme for Research and Training in Tropical Disease Research, along with the US National Institute of Allergy and Infectious Diseases and the European Economic Community, is fostering a "state of the art" research capacity in the developing world. Collaboration and exchange between re-

Joseph A. Cook, MD, MPH, is Director, Program in Tropical Disease Research, The Edna McConnell Clark Foundation, New York, New York.

Jeffrey W. Mecaskey, MSc, is Associate Director, Program in Tropical Disease Research, The Edna McConnell Clark Foundation, New York, New York.

ABBREVIATIONS USED:

BCG: Bacillus Calmette-Guerin
DNA: deoxyribose nucleic acid
GST: glutathione-S-transferase
TPI: triose phosphate isomease
UNDP: United Nations Development Program
WHO: World Health Organization

search facilities in industrialized countries capable of the most recent molecular biology and the laboratories and programs where this research must be applied have improved control by strengthening the link between research and application. The best bench research is informed by and relevant to the problems of the bedside or the fieldsite where disease control is needed.

Following a somewhat artificial dichotomy, speculation of future directions for schistosomiasis research and control will continue according to laboratory and field application.

The basic aspect of the schistosome's relationship to the human host – how it evades the human immune response . . . remains a central question in immunological research.

The Laboratory

Laboratory research in schistosomiasis will continue to be dominated by molecular biology and immunology. Parasite biology, particularly study of schistosome anatomical and biochemical transition, will be enhanced by molecular biology in an attempt to characterize the genes that direct the parasite's complex life cycle. The basic aspect of the schistosome's relationship to the human host – how it evades the human immune response while existing intravascularly for an average of five to seven years – remains a central question in immunological research and will continue to provide a focus for laboratory investigation in coming years. At the same time, human studies on the dynamics of infection are eattempting to identify which parts of the human immune responses are responsible for resistance to re-infection.

Human immune studies and their comparable animal studies may be expected to focus on cellular responses and cellular immunity's role both in protective immunity and in immunopathology. To the extent that these studies can guide vaccine development, antigens will be selected on the basis of their ability to stimulate a protective cellular response without inducing deleterious immunopathologic reactions. Studies that have so far revealed much about granuloma formation and fibrogenesis in the liver can be expected to continue to contribute to the development of a safe and protective vaccine.

Over 30 protective schistosome antigens have been identified, yet in animal models the level of protection induced by any antigen continues to hover around 50%. Studies are being undertaken now to determine what effect combinations of some of these antigens might provoke in experimental animals. Studies on these antigens, and perhaps some new ones, can be expected to increase over the coming years as more is learned about which antigens stimulate the proper immune response and how they can be modified and enhanced by the appropriate adjuvant. Antigens under consideration fall into several categories: surface antigens (usually isolated from the surface of the schistosomule, which is thought to be a prime candidate for attack); muscle proteins (paramyosin, myosin, and tromyosin); enzymes involved in energy generation, particularly triose phosphate isomerase (TPI); glutathione- and peroxide-metabolizing enzymes, particularly glutathione-S-transferase (GST); heat shock proteins; and proteinases, including both elastase and hemoglobinase. The latter enzyme, so long a focus of Senft's attention,[3] may yet be utilized in vaccine studies as well as immunodiagnosis. The 26 kilodalton iso-enzyme of GST is being produced currently by Transgéne of Pasteur Merieux in France in pure form, with the intention of launching phase I toxicity trials in humans within the next year. While new antigens may indeed be found, it is unlikely that there will be a single-antigen vaccine; more likely it will be a mixture of antigens. Research is still required to discover the best mode of antigen presentation and the means to enhance the immune response through use of new adjuvants and/or novel presentation. If we know the right antigen(s) to induce protection, can their genes be inserted into CG and administered in ongoing vaccination programs before the child toddles into the stream to acquire the first schistosome?

. . . antigens will be selected on the basis of their ability to stimulate a protective cellular response without inducing deleterious immunopathologic reactions.

The Field

The availability of praziquantel, a single-dose, safe, and effective antischistosomal compound, together with our increased understanding of the epidemiology of the disease, have changed the direction of control activities in much the same way that the advance in molecular biology have changed bench and animal model-related research. Although its mechanism is not completely understood, praziquantel results in a strenuous muscle contraction, causing the worm to release its hold, cease metabolic activity, and in all likelihood be killed by human immune responses. Several field studies have shown that chemotherapy with the drug is the most cost-effective means of controlling schistosomiasis. Other research in both *S. mansoni*- and *S. haematobium*-endemic areas has shown that chemotherapy applied only to school-aged children reduces morbidity in the population that has the greatest parasite burden and is most likely to manifest clinical disease. At the same time, attention to this population will exert a downward pressure on the intensity-of-infection distribution and will reduce egg excretion and subsequent re-infection. There is general agreement that we have the means to control severe disease due to schisto-

somiasis if we could only apply the appropriate, available control measures.

There is general agreement that we have the means to control severe disease due to schistosomiasis if we could only apply the appropriate, available control measures.

In terms of disease control, it is clear that the use of chemotherapy has not expanded to the extent that it should if morbidity and mortality due to schistosome infection are to be reduced. The coming years will undoubtedly see an expansion of this work, with focus first on urinary schistosomiasis, which can be more easily detected and the response to treatment measured. There is evidence that control strategies employing chemotherapy benefit not only those with heavy infections and clinical disease but also those with light infections and no apparent clinical signs. Studies in areas endemic for the three major human schistosomes have demonstrated an association between schistosomiasis and impaired growth and development in children. There is evidence of striking reversal with treatment. More studies to document this as well as measure an impact on exercise tolerance, learning, and cognitive development are needed.

Whether the consequence of increased use of praziquantel in the field in large-scale control programs will result in the occurrence of drug-resistant schistosoma strains has already been the subject of experimentation in a number of laboratories. Although several cases have been cited for tolerance or resistance to hycanthone and oxamniquine, there has so far not been a single report documenting tolerance or resistance to praziquantel. Reports from the field have not been verified when the purportedly resistant strains were isolated and tested in experimental animals. Clearly, the expanded use of praziquantel dictates that we should be alert to the emergence of resistance, and appropriate laboratory studies must be carried out or integrated into large-scale control programs.

But, beyond simply having the means to control schistosomiasis available, the focus must include integrating control activities in to general public health and primary health care programs. Successful control relies on good management, organization, logistics and surveillance. There are many operational research questions that need to be answered to control schistosomiasis cheaply and effectively. The focus on the school-aged population offers an opportunity to integrate schistosomiasis control with treatment of other helminth infections and perhaps micro-nutrient replacement as well. Because this population, or at least a great part of it in most countries, can be reached through schools, integration of the work of ministries of health and education will be essential. Groundwork for such a "partnership for the health of the school-aged child" took place at the Bellagio Conference Center in August, 1991.[4]

In his recent book, *Bilharzia: A History of Imperial Tropical Medicine*, John Farley raises the important question, "Who has benefited most from this (schistosomiasis research) activity, the *fellaheen* in Egypt, or the academics in the United States where most of the research takes place?"[5] While numerous examples can be cited where esoteric research much later had profound public health benefits, such a provocative question needs to be kept always before us. Our speculation is that the next twenty years in schistosomiasis research will see much stronger efforts to apply what we learn in areas where the disease exists and to link laboratory research to the questions most relevant to the health of the *fellaheen* in Egypt.

References

1. Hoffman DB and Warren KS, eds. Schistosomiasis IV Condensations of the Selected Literature 1963-1975. Washington, DC: Hemisphere Publishing Corporation, 1978.
2. Senft AW. Consideration of Schistosome Physiology in the Search for Anti-bilharziasis Drugs. Annals of New York Academy of Science 1969; 160:571-592.
3. Senft AW, Goldberg MW, Byram JE and Jaivan JS. Schistosomal Hemoglobinase: Nature of the Protease and Implications of the Host. In van den Bossche H (ed.) The Host Invader Interplay, Amsterdam: Elsevier/North Holland Biomedical Press pp. 427-442, 1980.
4. Berkley S and Jamison D. A Conference on the Health of School-age Children. Summary report available from the Rockefeller Foundation, 1133 Avenue of the Americas, New York, NY 10036.
5. Farley John. Bilharzia: A History of Imperial Tropical Medicine. Cambridge Massachusetts: Cambridge University Press, p. 301, 1991.

Address correspondence to:
Joseph A. Cook, MD, MPH, Director
Program in Tropical Disease Research
The Edna McConnell Clark Foundation
250 Park Avenue
New York, New York 10177-0028

Rural Health CARING for the country

National Rural Health Association
15th Annual Conference on Rural Health
May 6–9, 1992
Hyatt Regency Crystal City
Washington, DC

Rx C3: Coughs, Colds, Flu...

NDC 0372-0048-16 ONE PINT (473.2 ml.)

S-T FORTE™

SUGAR-FREE
ALCOHOL-FREE

(Revised Formula 1-92)
Each 5ml. contains:
HYDROCODONE BITARTRATE U.S.P. .....2.50 mg.
CHLORPHENIRAMINE MALEATE U.S.P. .....2.0 mg.

CIII

Antitussive Antihistamine

CAUTION: Federal law prohibits dispensing without a prescription.

Does not contain: sugar, alcohol, dyes, saccharin, sorbitol, decongestants, mannitol, or xylitol.

Complete information in the package.

Tel. (401) 942-8555 or 942-8556
Toll Free 1 (800) 638-SCOT

™ Trade Mark since 1956

SCOT-TUSSIN®
PHARMACAL CO., INC.
CRANSTON, RI 02920-0217 (USA)

Approved for payment by Medical Assistance 1/92

The Rhode Island Optometric Association

in conjunction with

The American Diabetes Association, RI Affiliate and Ocean State Physician's Health Plan

presents a symposium for

Medical Doctors and other Health Professionals

Ocular Complications and Management of the Diabetic Patient

APRIL 29, 1992
8:00 a.m. - 12:30 p.m.

HOLIDAY INN AT THE CROSSING
RT 5, WARWICK, RI
To obtain a program, in RI call (800) 491-7550.
Outside RI, (401) 461-7550 or FAX (401) 941-5979
CME available thru American Diabetes Assoc.

YOCON®
YOHIMBINE HCl

Description: Yohimbine is a 3a-15a-20B-17a-hydroxy Yohimbine-16a-carboxylic acid methyl ester. The alkaloid is found in Rubaceae and related trees. Also in Rauwolfia Serpentina (L) Benth. Yohimbine is an indolalkylamine alkaloid with chemical similarity to reserpine. It is a crystalline powder, odorless. Each compressed tablet contains (1/12 gr.) 5.4 mg of Yohimbine Hydrochloride.

Action: Yohimbine blocks presynaptic alpha-2 adrenergic receptors. Its action on peripheral blood vessels resembles that of reserpine, though it is weaker and of short duration. Yohimbine's peripheral autonomic nervous system effect is to increase parasympathetic (cholinergic) and decrease sympathetic (adrenergic) activity. It is to be noted that in male sexual performance, erection is linked to cholinergic activity and to alpha-2 adrenergic blockade which may theoretically result in increased penile inflow, decreased penile outflow or both.

Yohimbine exerts a stimulating action on the mood and may increase anxiety. Such actions have not been adequately studied or related to dosage although they appear to require high doses of the drug. Yohimbine has a mild anti-diuretic action, probably via stimulation of hypothalmic centers and release of posterior pituitary hormone.

Reportedly, Yohimbine exerts no significant influence on cardiac stimulation and other effects mediated by B-adrenergic receptors, its effect on blood pressure, if any, would be to lower it, however no adequate studies are at hand to quantitate this effect in terms of Yohimbine dosage.

Indications: Yocon® is indicated as a sympathicolytic and mydriatric. It may have activity as an aphrodisiac.

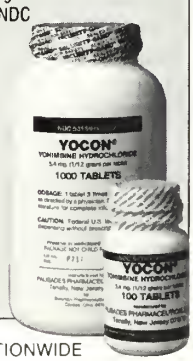
Contraindications: Renal diseases, and patient's sensitive to the drug. In view of the limited and inadequate information at hand, no precise tabulation can be offered of additional contraindications.

Warning: Generally, this drug is not proposed for use in females and certainly must not be used during pregnancy. Neither is this drug proposed for use in pediatric, geriatric or cardio-renal patients with gastric or duodenal ulcer history. Nor should it be used in conjunction with mood-modifying drugs such as antidepressants, or in psychiatric patients in general.

Adverse Reactions: Yohimbine readily penetrates the (CNS) and produces a complex pattern of responses in lower doses than required to produce peripheral a-adrenergic blockade. These include, anti-diuresis, a general picture of central excitation including elevation of blood pressure and heart rate, increased motor activity, irritability and tremor. Sweating, nausea and vomiting are common after parenteral administration of the drug.[1,2] Also dizziness, headache, skin flushing reported when used orally.[1,3]

Dosage and Administration: Experimental dosage reported in treatment of erectile impotence.[1,3,4] 1 tablet (5.4 mg) 3 times a day, to adult males taken orally. Occasional side effects reported with this dosage are nausea, dizziness or nervousness. In the event of side effects dosage to be reduced to ½ tablet 3 times a day, followed by gradual increases to 1 tablet 3 times a day. Reported therapy not more than 10 weeks.[3]

How Supplied: Oral tablets of Yocon® 1/12 gr. 5.4 mg in bottles of 100's NDC 53159-001-01 and 1000's NDC 53159-001-10.



References:

1. A. Morales et al., New England Journal of Medicine: 1221, November 12, 1981.
2. Goodman, Gilman — The Pharmacological basis of Therapeutics 6th ed., p. 176-188. McMillan December Rev. 1/85.
3. Weekly Urological Clinical letter, 27:2, July 4, 1983.
4. A. Morales et al., The Journal of Urology 128: 45-47, 1982.

Rev. 1/85

AVAILABLE AT PHARMACIES NATIONWIDE

PALISADES PHARMACEUTICALS, INC.
219 County Road
Tenafly, New Jersey 07670
(201) 569-8502
1-800-237-9083

NURSE ANESTHESIA SERVICES OF NEW ENGLAND (NASNE)

serving Rhode Island hospitals with local CRNAs

- Specialists in TEMPORARY and PERMANENT placement of CRNAs
- NASNE provides local, experienced, highly-qualified CRNAs to Rhode Island hospitals
- NASNE's use of local CRNAs reduces your staffing costs by avoiding travel and other associated expenses
- Dependable and personalized service is provided by a staff that understands you and your scheduling needs

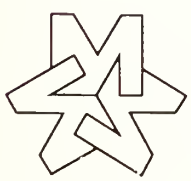
NASNE – the Rhode Island Specialists
Call us at 1-800-531-5319

A critical health problem for your patient. A difficult problem for you to treat.

The Miriam Hospital Weight Management Service offers treatment programs addressing all levels of obesity. With over 10 years' experience in obesity treatment and research, our multidisciplinary team provides the resources needed for safe, medically monitored weight loss and for long-term success in maintaining weight loss.

For more information on our programs, or to refer a patient, call:
(401) 861-0870

Portions of our programs may be covered by health insurance.



The Miriam Hospital Weight Management Service
Division of Behavioral Medicine
An affiliate of the Brown University Medical School

HEALTH BY NUMBERS

Rhode Island
Department of Health
Barbara A. DeBuono, MD, MPH
Director of Health

Rhode Island's Lead in School and Preschool Drinking Water Program

In response to the Lead Contamination Control Act of 1988, the Office of Environmental Health Risk Assessment (OEHRA) and the Division of Drinking Water Quality of the Rhode Island Department of Health began a program in January 1990 to monitor and reduce lead in school and preschool drinking water. The program offered: 1) educational materials for school, preschool and day-care facility officials, 2) free testing for lead in drinking water (although officials were encouraged to use private laboratories), and 3) recommendations for reducing the lead content of drinking water based on testing results.

Reliance on voluntary compliance was sufficient to achieve testing of drinking water at 85% of schools and 54% of preschools and day-care facilities (Table 1). About half of these facilities relied on the Department of Health to provide free testing. Lead was found to be pervasive in school, preschool and day-care drinking water (Figure 1). Nearly 70% of tested facilities had at least one tap that exceeded 5 ppb, the Department of Health's advisory level. Of these facilities with elevated lead levels, more than half had at least one tap with lead levels exceeding the US Environmental Protection Agency's action level of 20 ppb.

In May and June of 1991, the OEHRA conducted a telephone survey to determine the extent to which school, preschool and day-care facility officials were following OEHRA recommendations for reducing children's exposures to lead in drinking water (Figure 2). Only 15% of the facilities surveyed had made no response whatsoever to the contamination problems or had relied solely on notification of parents; the vast majority had instituted one or more appropriate measures to control lead in drinking water. Flushing was by far the most common measure taken to reduce lead levels in drinking water, but replumbing and shutting off taps were also commonly used strategies to reduce exposures, especially for taps with lead levels exceeding 20 ppb.

In addition to reducing children's exposures to lead in drinking water, this program has had a valuable public education impact. The intense public and media attention focused on the lead in school and preschool drinking water program has provided numerous opportunities for comprehensive public education about childhood lead poisoning.

No other state in New England has achieved such widespread testing and remediation of lead hazards associated with drinking water in schools and preschools. The OEHRA is conducting follow-up activities to ensure that drinking water at all Rhode Island child care facilities have acceptable levels of lead.

Table 1. **Day care facilities, preschools and schools in Rhode Island in compliance with recommendations for testing lead in drinking water by September 1991.**

Type of Facility	Tested	Total	%
Day Care/Preschool			
Day care centers & preschools	117	217	54
Home day care, etc.	49	NA*	NA*
Schools			
Elementary	251	283	89
Secondary	101	132	77
Total	352	412	85

*NA – Not available

Submitted by the Office of Environmental Health Risk Assessment, Robert R. Vanderslice, PhD, Principal Toxicologist, Bela T. Matyas, MD, MPH, Chief. Health by Numbers *is edited by Jay S. Buechner, PhD, and William J. Waters, Jr, PhD.*

Figure 1. **Lead contamination of drinking water at Rhode Island day care facilities and schools determined in first draw samples, 1990 and 1991**

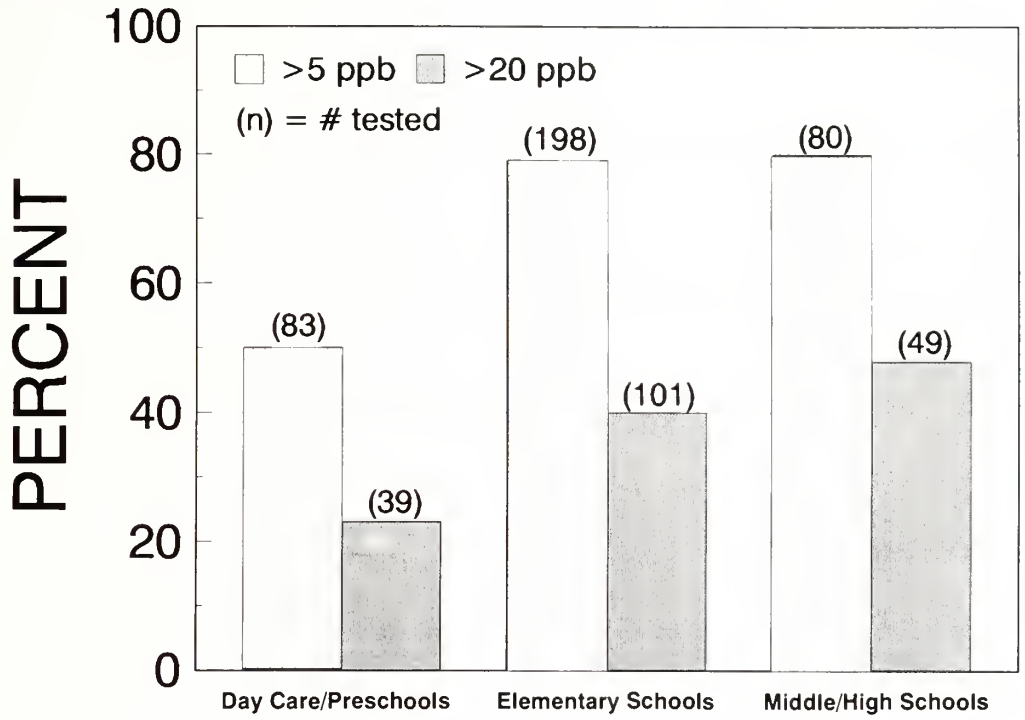
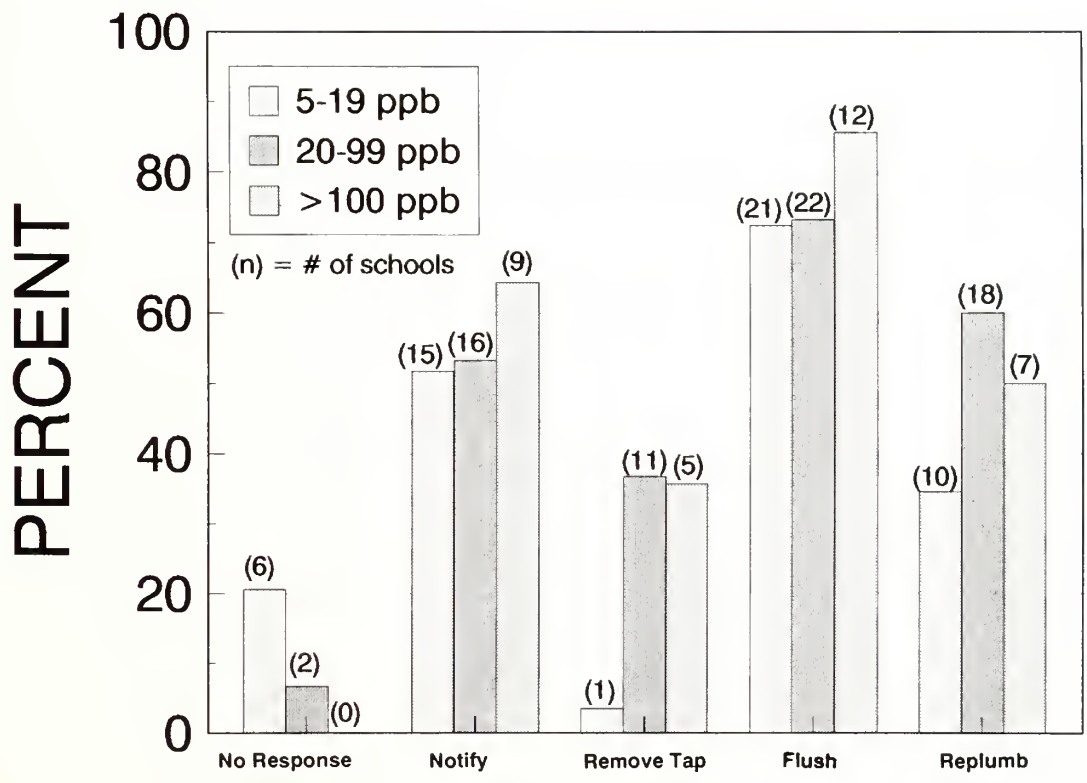


Figure 2. **Rate of compliance at schools with recommendations for reducing lead content in drinking water, Summer 1991.**



QUESTION:

WHAT ARE THE THREE MOST IMPORTANT THINGS TO CONSIDER WHEN CHOOSING AN INSURANCE AGENCY?

ANSWER:

EXPERIENCE, EXPERIENCE, EXPERIENCE

INSURANCE SINCE 1879

STARKWEATHER & SHEPLEY INC. - (401) 421-6900

Morton Smith, Inc. - (401) 861-6800

155 South Main Street
Providence, Rhode Island 02903

THE RHODE ISLAND MEDICAL JOURNAL

The Official Organ of the Rhode Island Medical Society
Issued Monthly under the direction of the Publication Committee

VOLUME 1
NUMBER 1

PROVIDENCE, R. I., JANUARY, 1917

PER YEAR $2.00
SINGLE COPY, 25 CENTS

THE RHODE ISLAND MEDICAL JOURNAL HERITAGE

Ninety Years Ago
(March, 1902)

ED Chesebro, MD writes a personal essay on the treatment of pneumonia. He notes that for centuries pneumonia has been the battle ground of medical therapeutics. In the immediate past, the therapeutic interventions have consisted of venesection, antimony, calomel, veratrum viride, digitalis, quinine and " . . . a host of other remedies which have, for a time, been vaunted as specifics." He then quotes Osler on the irrelevancies of these agents. Osler said: "Pneumonia is a self limited disease and runs its course uninfluenced in any way by medicine. It can neither be aborted nor cut short by any known means at our command. Even under the most unfavorable circumstances, it will terminate abruptly and naturally without a dose of medicine having been administered."

The author lists some newer forms of therapy but his advocacies lack enthusiasm for any of the interventions. He mentions inhalation of steam impregnated with creosote as of marginal value. Similarly counter-irritants such as mustard, turpentine or hot poultices may have some occasional application. Cold applications on the chest may, or may not, be of help. Pain, restlessness or excessive cough may yield to opium. Heroin, he states, is a satisfactory hypnotic. Temperature control is important in reducing some of the cerebral complications of pneumonia, such as convulsions.

Stimulation with whiskey or strichnia has only limited merit he states. Some heart stimulants such as digitalis or nitroglycerine may be employed. In some cases the subcutaneous clysis of saline solution can aid the patient. No mention is made of the bacteriologically discrete forms of pneumonia other than those caused by the pneumococcus.

The author concludes with the following set of eight recommendations: "Place the patient under the most favorable hygienic conditions with special reference to ventilation. Carefully regulate the diet, guarding against constipation, and insisting upon the liberal use of pure cool water. Early in the course of the disease employ counter-irritants, particularly in the bronchopneumonia of children. Relieve distressing cough by inhalations and if necessary by the use of opium or its derivatives. Relieve pleuritic pain by the intermittent use of hot or ice poultices or by the subcutaneous use of morphia. Reduce temperature, if necessary, by bathing. Stimulate the heart with strichnine and in selected cases with alcohol, digitalis and normal salt solution. It is possible that venesection, which may be followed immediately by the injection of normal salt solution, is indicated in certain cases of engorged right heart and if boldly done may be instrumental in saving life. Employ large and frequently repeated doses of antipneumococcic serum in desperate cases, particularly in those with a tendency to extension of the inflammatory process."

An article by Donald Churchill, MD describes the early history of medicine in Rhode Island, particularly health care events in the seventeenth and eighteenth centuries. He notes that some pestilence decimated the Indian tribes of southern New England just prior to the landing of the Pilgrims. Cotton Mather, who hated the local Aborigines, describes the situation thus: "The Indians in these parts had newly, even about a year or two before, been visited with such a prodigious Pestilence; as carried away not a tenth, but nine parts in ten (yea tis said nineteen of twenty) among them; so that the woods were almost cleared of these pernicious creatures to make room for a better growth." Most believed that the pestilence was smallpox.

The first known physician in Roger Williams' settlement was John Clark who had been expelled from Boston and then migrated to Portsmouth in 1639. He returned to England for many years but finally returned to Newport where he officiated as pastor of the First Baptist Church while continuing his medical practice.

While there was no general licensing of physicians in the early days,

something which was "strenuously resisted in Rhode Island by those who insisted that it was a dangerous innovation, and an unjustifiable interference with individual liberty", the General Assembly of the state occasionally granted authorization to practice both "physsicke and chirurgery" to some individuals deemed qualified. In 1664, the Assembly granted such permission to Captain John Cranston of Newport (the city of Cranston is named after this practitioner). The author also describes the famous Bowen family beginning with Dr Richard Bowen who practiced medicine in Seekonk. His sons and grandsons continued in the tradition of medicine both in Providence and in neighboring communities. One of the Bowens became interested in the bleaching properties of chlorine, but developed lung disease from contact with the substance and died in his thirtieth year. His experiments nevertheless formed the basis for the fabric bleaching industries of Rhode Island during the nineteenth century.

The article concludes with a roster of prominent Rhode Island physicians including Waterhouse, Senter, Bowens, Throop, Wheaton, Drowne, and Fiske. "Let us then honor the inheritance of such examples with the hope that in the years to come, our names may be added to those already on Rhode Island's list of worthies . . ."

Fifty Years Ago
(April, 1942)

The leading article by JM Beardsley, MD is entitled "The Treatment of Pleural and Pulmonary Suppuration." The study summarizes seven years of experience by the author at the Charles V. Chapin Hospital and includes 180 cases of acute empyema, 102 cases of lung abscess and 65 cases of bronchiectasis. Amongst the empyema series the mortality rate was 16%. The author discusses the advantages and shortcomings of various surgical approaches including direct aspiration, closed drainage, and open drainage. He emphasizes that the drainage should emanate from the most dependent point of the cavity, which can often be determined by lipiodol installation followed by X-ray examination. He notes that sulfonamide solution irrigation has been used "with no apparent increased benefit." In their series of lung abscess, the mortality rate was 30%. Accurate localization, in the opinion of the author, is of prime importance in successful intervention. The author describes briefly the surgical approaches to the problem of bronchiectasis, discouraging the use of a two-stage procedure. He concludes: "X-ray treatment for bronchiectasis in our experience has been of little or no value."

A symposium of the experimental, surgical and medical aspects of hypertension is published, with articles by Drs Morgan Cutts, Robert Baldridge and Clifton Leech. Therapies including surgical sympathectomy, thiocyanate therapy, and injections of renal antipressor substances are evaluated.

Eric Stone, MD describes the Rhode Island Hospitals' Army Unit which is in the process of assemblage. The unit, officially the 48th Evacuation Hospital, will be comprised of about 28 commissioned physicians, 2 dentists, 60 nurses, and about 320 enlisted personnel. With regular army administrators, the hospital complement will be 417 and will service about 400 beds. The unit is described as a "hybrid offspring born of the union of an operating floor and a travelling circus." It is designed and equipped to be either set up or taken down within 24 hours for movement forward or back with fluctuations in the combat zone. The X-ray equipment, laboratory and sterilizing units are kept in specially designed trucks. The date of mobilization of the hospital unit is not known at the time of printing.

The lead editorial entitled "Keeping Informed" lists the many ways in which the practicing physicians of Rhode Island are kept abreast of the military situation both in the states and in England. "Rhode Island physicians hope for further opportunities of hearing first hand what has been done elsewhere and what must be done in this country if organized medicine is to do its part in defensive and offensive warfare."

A second editorial discusses the sale of the Chapin Hospital to the State of Rhode Island and its future use for inpatient therapies.

Twenty-Five Years Ago
(April, 1967)

The lead article discusses changing concepts in the surgical management of hemorrhagic gastritis, with particular reference to the use of vagotomy and pyloroplasty. The author is Francis Catanzaro, MD. Hemorrhagic gastritis, the author notes, is a relatively uncommon cause of major gastrointestinal bleeding requiring surgical intervention. While its etiology is varied, it is more commonly associated with heavy alcoholic intake. It is not uncommon in patients on heavy doses of acetylsalicylic acid-containing compounds, indocin or butazolidin. The author describes three cases effectively treated by vagotomy and pyloroplasty. Mary Efron, MD writes on the metabolic factors in the prevention of mental retardation, with particular attention to inherited amino acid disorders and fatty acid inborn errors of metabolism. The author concludes: "Screening programs have thus enormously increased both our knowledge and our awareness of our ignorance. The experience with massive PKU screening in particular has indicated that we know very little about inborn errors of metabolism. Certainly, the simple concepts which were the basis of the compulsory legislation for PKU are open to question. It is hoped that we can pursue our course of investigation of the other inborn errors of metabolism without imposition of compulsory screening programs which necessarily lead to treatment by inexperienced persons and which necessarily imply that there is an effective tried and true therapy which must be administered as soon as the diagnosis is made. Our state of knowledge about the best treatment for these disorders is as primitive as that about the pathophysiology of the diseases."

Alton Paull, MD and Sharad Deshpande, MD offer a case report of atrial flutter with complete AV block due to digitalis toxicity and controlled by withholding digitalis. They note in reviewing the relevant literature that they were " . . . unable to find a previous report of a case manifesting a combination of atrial flutter and AV block due to digitalis. In the presence of digitalis toxicity associated with complete AV block potassium administration is contraindicated even in the presence of hypokalemia."

Joseph Baker, MD chairs a panel discussion of drugs which affect human behavior. His brief commentary touches upon such classical and modern agents as alcohol, morphine, barbiturates, peyote bean, LSD, the phenothiazines and rauwolfia compounds. He notes that " . . . an estimated 50,000,000 patients have been treated with the phenothiazines. In addition, some 10,000 papers have been written describing the tranquilizers."

Need Information about Businesses?
Call the Business *INFOLINE!*

There are over 9 million businesses in the U.S. – and finding information about them can be virtually impossible, especially when you need it *fast*. But now there's a way . . . a revolutionary new service called *Business INFOLINE!* Need to know the address and phone number for "XYZ Company" somewhere in Florida, or the name and phone number of a "Cadillac Dealer" in Palm Beach? Even telephone company directory assistance can't help you in these situations . . . but we can!

For example . . .

"Your BMW breaks down on the interstate, and you need to know if there 's a dealer in the next town."

"An out-of-town company is trying to sell you vinyl siding for your house and you need more information about them – how long the company has been in business, and how many employees they have."

"You're planning a vacation in the Pacific Northwest, and you want to line up things for the kids to do. So you need to find the amusement parks and zoos in Oregon and Washington."

"A friend gave you a tip that "Apex Industries" would be a good investment, but you want to know more. What do they do? What are their approximate annual sales?"

The Business INFOLINE is indispensable for home or office? And the cost is *only* $3.00 for the first minute and $1.50 for each additional minute, conveniently billed to your phone number. The service is available Monday through Friday, 7:00 a.m. to 6:00 p.m., Central Time.

Dial 1-900-896-0000

Ask for Ext. #195

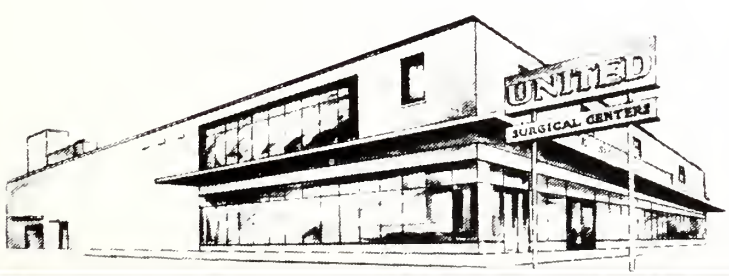
Money-back Guarantee if not satisfied.

A Service of American Business Information • 5711 So. 86th Circle • Omaha, NE 68127

There must be a good reason why we've become the trusted back-up resource for more Rhode Island doctors (and their patients) than anyone else.

UNITED SURGICAL CENTERS

The Professionals in Home Health Care Equipment



We carry just about EVERYTHING for Home Health Care which means, everything a patient or convalescent needs to implement the doctor's treatment directions. For Ostomy and Oxygen needs to Orthopedic Appliances, Wheelchairs, Walkers and Hospital Beds, we're here to serve your patients. Our staff is knowledgeable and dedicated to supplying exactly "what the doctor ordered". We've been doing it dependably for many years.

That's how we've earned the trust of so many doctors.

Medicare and Third Party Claims Accepted and Processed.

380 WARWICK AVE., WARWICK
781-2166

Unpaid Receivables Can Make You Sick.

This Will Make You Feel Better.

The longer you wait to collect, the less your receivables are worth. I.C. System handles more health care debts than any other collection agency in the country and offers:

- Competitive rates and local representation
- Expert collection practices sensitive to health care issues
- Listing of unpaid debts with national credit reporting agencies
- Endorsements from over 1,000 business and professional associations and societies

When it comes to unpaid receivables, I.C. System makes speedy recoveries. Call us today.

1-800-325-6884

An Approved Membership Service of the Rhode Island Medical Society

I.C. System
The System Works®

© 1990 I.C. System, Inc.
#3382-1 9/90

The ACCUPRIL Single-Agent Commitment™

Parke-Davis is confident that for many of your hypertensive patients ACCUPRIL will achieve the decrease in blood pressure you expect.

If, in your medical judgment, your patient requires a diuretic in addition to ACCUPRIL at any time during ACCUPRIL therapy, Parke-Davis will refund your patient's cost of the diuretic.*†

New!

ONCE-A-DAY‡

ACCUPRIL®™

quinapril HCl tablets 10, 20, 40 mg

* See DOSAGE AND ADMINISTRATION section of prescribing information.

† If, after an adequate trial of ACCUPRIL alone, based on your medical judgment as the prescribing physician, you determine that your patient requires the addition of a diuretic, Parke-Davis will refund to the patient his/her cost for the diuretic prescription less any amount reimbursed or paid for by an HMO, insurance company, or any other plan or program.

For more details, ask your Parke-Davis Representative or call 1-800-955-3077.

‡ In some patients, the antihypertensive effect may diminish toward the end of the once-daily dosing interval. In such patients, an increase in dosage or twice-daily administration may be warranted.

ACCUPRIL is available in 10, 20, and 40 mg tablets. Usual initial starting dosage is 10 mg once daily.

ACCUPRIL is contraindicated in patients who are hypersensitive to this product and in patients with a history of angioedema related to previous treatment with an ACE inhibitor.

Please see brief summary of prescribing information on following page.

© 1991 Warner-Lambert Company

PARKE-DAVIS

Accupril® (Quinapril Hydrochloride Tablets)

Before prescribing, please see full prescribing information. A brief summary follows.

INDICATIONS AND USAGE

ACCUPRIL is indicated for the treatment of hypertension. It may be used alone or in combination with thiazide diuretics.

In using ACCUPRIL, consideration should be given to the fact that another angiotensin-converting enzyme (ACE) inhibitor, captopril, has caused agranulocytosis, particularly in patients with renal impairment or collagen vascular disease. Available data are insufficient to show that ACCUPRIL does not have a similar risk (see WARNINGS).

CONTRAINDICATIONS

ACCUPRIL is contraindicated in patients who are hypersensitive to this product and in patients with a history of angioedema related to previous treatment with an ACE inhibitor.

WARNINGS

Angioedema: Angioedema of the face, extremities, lips, tongue, glottis, and larynx has been reported in patients treated with ACE inhibitors and has been seen in 0.1% of patients receiving ACCUPRIL. Angioedema associated with laryngeal edema can be fatal. If laryngeal stridor or angioedema of the face, tongue, or glottis occurs, treatment with ACCUPRIL should be discontinued immediately, the patient treated in accordance with accepted medical care, and carefully observed until the swelling disappears. In instances where swelling is confined to the face and lips, the condition generally resolves without treatment, although antihistamines may be useful in relieving symptoms.

Where there is involvement of the tongue, glottis, or larynx likely to cause airway obstruction, emergency therapy including, but not limited to, subcutaneous epinephrine solution 1:1000 (0.3 to 0.5 mL) should be promptly administered (see ADVERSE REACTIONS).

Hypotension: Symptomatic hypotension was rarely seen in uncomplicated hypertensive patients treated with ACCUPRIL but, as with other ACE inhibitors, it is a possible consequence of therapy in salt/volume depleted patients, such as those previously treated with diuretics or dietary salt restriction or who are on dialysis (see PRECAUTIONS, DRUG INTERACTIONS, and ADVERSE REACTIONS). In controlled studies, syncope was observed in 0.4% of patients (N = 3203), this incidence was similar to that observed for captopril (1%) and enalapril (0.8%).

In patients with concomitant congestive heart failure, with or without associated renal insufficiency, ACE inhibitor therapy may cause excessive hypotension, which may be associated with oliguria or azotemia and, rarely, with acute renal failure and death. In such patients, ACCUPRIL therapy should be started at the recommended dose under close medical supervision. These patients should be followed closely for the first 2 weeks of treatment and whenever the dosage of antihypertensive medication is increased (see DOSAGE AND ADMINISTRATION).

If symptomatic hypotension occurs, the patient should be placed in the supine position and, if necessary, normal saline may be administered intravenously. A transient hypotensive response is not a contraindication to further doses, however, lower doses of ACCUPRIL or reduced concomitant diuretic therapy should be considered.

Neutropenia/Agranulocytosis: Another ACE inhibitor, captopril, has been shown to cause agranulocytosis and bone marrow depression rarely in patients with uncomplicated hypertension, but more frequently in patients with renal impairment, especially if they also have a collagen vascular disease such as systemic lupus erythematosus or scleroderma. Agranulocytosis did occur during ACCUPRIL treatment in one patient with a history of neutropenia during previous captopril therapy. Available data from clinical trials of ACCUPRIL are insufficient to show that, in patients without prior reactions to other ACE inhibitors, ACCUPRIL does not cause agranulocytosis at similar rates. As with other ACE inhibitors, periodic monitoring of white blood cell counts in patients with collagen vascular disease and/or renal disease should be considered.

Fetal/Neonatal morbidity and mortality: ACE inhibitors, including ACCUPRIL, can cause fetal and neonatal morbidity and mortality when administered to pregnant women.

When ACE inhibitors have been used during the second and third trimesters of pregnancy, there have been reports of hypotension, renal failure, skull hypoplasia, and death. Oligohydramnios has also been reported, presumably resulting from decreased fetal renal function; oligohydramnios has been associated with fetal limb contractures, craniofacial deformities, hypoplastic lung development, and intrauterine growth retardation.

Prematurity and patent ductus arteriosus have been reported, although it is not clear whether these occurrences were due to the ACE-inhibitor exposure or to the mother's underlying disease. It is not known whether exposure limited to the first trimester can adversely affect fetal outcome.

A patient who becomes pregnant while taking ACE inhibitors, or who takes ACE inhibitors when already pregnant, should be apprised of the potential hazard to her fetus. If she continues to receive ACE inhibitors during the second or third trimester of pregnancy, frequent ultrasound examinations should be performed to look for oligohydramnios. When oligohydramnios is found, ACE inhibitors should generally be discontinued.

Infants with histories of in utero exposure to ACE inhibitors should be closely observed for hypotension, oliguria, and hyperkalemia. If oliguria occurs, attention should be directed toward support of blood pressure and renal perfusion. Hemodialysis and peritoneal dialysis have little effect on the elimination of quinapril and quinaprilat.

No fetotoxic or teratogenic effects were observed in rats at quinapril doses as high as 300 mg/kg/day (180 and 30 times the maximum daily human dose when based on mg/kg and mg/m², respectively), despite maternal toxicity at 150 mg/kg/day. Tested later in gestation and during lactation, reduced offspring body weight was seen at ≥25 mg/kg/day, and changes in renal histology (juxtaglomerular cell hypertrophy, tubular/pelvic dilation, glomerulosclerosis) were observed both in dams and offspring treated with 150 mg/kg/day. Quinapril was not teratogenic in the rabbit, however, as noted with other ACE inhibitors, maternal toxicity and embryotoxicity were seen in some rabbits at quinapril doses as low as 0.5 mg/kg/day (one time the recommended human dose) and 1.0 mg/kg/day, respectively.

PRECAUTIONS

General

Impaired renal function: As a consequence of inhibiting the renin-angiotensin-aldosterone system, changes in renal function may be anticipated in susceptible individuals. In patients with severe heart failure whose renal function may depend on the activity of the renin-angiotensin-aldosterone system, treatment with ACE inhibitors, including ACCUPRIL, may be associated with oliguria and/or progressive azotemia and rarely acute renal failure and/or death.

In clinical studies in hypertensive patients with unilateral or bilateral renal artery stenosis, increases in blood urea nitrogen and serum creatinine have been observed in some patients following ACE inhibitor therapy. These increases were almost always reversible upon discontinuation of the ACE inhibitor and/or diuretic therapy. In such patients, renal function should be monitored during the first few weeks of therapy.

Some hypertensive patients with no apparent preexisting renal vascular disease have developed increases in blood urea and serum creatinine, usually minor and transient, especially when ACCUPRIL has been given concomitantly with a diuretic. This is more likely to occur in patients with preexisting renal impairment. Dosage reduction and/or discontinuation of any diuretic and/or ACCUPRIL may be required.

Evaluation of hypertensive patients should always include assessment of renal function (see DOSAGE AND ADMINISTRATION).

Hyperkalemia and potassium-sparing diuretics: In clinical trials, hyperkalemia (serum potassium ≥5.8 mmol/L) occurred in approximately 2% of patients receiving ACCUPRIL. In most cases, elevated serum potassium levels were isolated values which resolved despite continued therapy. Less than 0.1% of patients discontinued therapy due to hyperkalemia. Risk factors for the development of hyperkalemia include renal insufficiency, diabetes mellitus, and the concomitant use of potassium-sparing diuretics, potassium supplements, and/or potassium-containing salt substitutes, which should be used cautiously, if at all, with ACCUPRIL (see PRECAUTIONS, Drug Interactions).

Surgery/anesthesia: In patients undergoing major surgery or during anesthesia with agents that produce hypotension, ACCUPRIL will block angiotensin II formation secondary to compensatory renin release. If hypotension occurs and is considered to be due to this mechanism, it can be corrected by volume expansion.

Information for Patients

Angioedema: Angioedema, including laryngeal edema, can occur with treatment with ACE inhibitors, especially following the first dose. Patients should be so advised and told to report immediately any signs or symptoms suggesting angioedema (swelling of face, extremities, eyes, lips, tongue, difficulty in swallowing or breathing) and to stop taking the drug until they have consulted with their physician (see WARNINGS).

Symptomatic hypotension: Patients should be cautioned that lightheadedness can occur, especially during the first few days of ACCUPRIL therapy, and that it should be reported to a physician. If actual syncope occurs, patients should be told to not take the drug until they have consulted with their physician (see WARNINGS).

All patients should be cautioned that inadequate fluid intake or excessive perspiration, diarrhea, or vomiting can lead to an excessive fall in blood pressure because of reduction in fluid volume, with the same consequences of lightheadedness and possible syncope.

Patients planning to undergo any surgery and/or anesthesia should be told to inform their physician that they are taking an ACE inhibitor.

Hyperkalemia: Patients should be told not to use potassium supplements or salt substitutes containing potassium without consulting their physician (see PRECAUTIONS).

Accupril® (Quinapril Hydrochloride Tablets)

Neutropenia: Patients should be told to report promptly any indication of infection (eg, sore throat, fever) which could be a sign of neutropenia.

NOTE: As with many other drugs, certain advice to patients being treated with ACCUPRIL is warranted. This information is intended to aid in the safe and effective use of this medication. It is not a disclosure of all possible adverse or intended effects.

Drug Interactions

Concomitant diuretic therapy: As with other ACE inhibitors, patients on diuretics, especially those on recently instituted diuretic therapy, may occasionally experience an excessive reduction of blood pressure after initiation of therapy with ACCUPRIL. The possibility of hypotensive effects with ACCUPRIL may be minimized by either discontinuing the diuretic or cautiously increasing salt intake prior to initiation of treatment with ACCUPRIL. If it is not possible to discontinue the diuretic, the starting dose of quinapril should be reduced (see DOSAGE AND ADMINISTRATION).

Agents increasing serum potassium: Quinapril can attenuate potassium loss caused by thiazide diuretics and increase serum potassium when used alone. If concomitant therapy of ACCUPRIL with potassium-sparing diuretics (eg, spironolactone, triamterene, or amiloride), potassium supplements, or potassium-containing salt substitutes is indicated, they should be used with caution along with appropriate monitoring of serum potassium (see PRECAUTIONS).

Tetracycline and other drugs that interact with magnesium: Simultaneous administration of tetracycline with ACCUPRIL reduced the absorption of tetracycline by approximately 28% to 37%, possibly due to the high magnesium content in ACCUPRIL tablets. This interaction should be considered if coprescribing ACCUPRIL and tetracycline or other drugs that interact with magnesium.

Lithium: Increased serum lithium levels and symptoms of lithium toxicity have been reported in patients receiving concomitant lithium and ACE inhibitor therapy. These drugs should be co-administered with caution, and frequent monitoring of serum lithium levels is recommended. If a diuretic is also used, it may increase the risk of lithium toxicity.

Other agents: Drug interaction studies of ACCUPRIL with other agents showed:

- Multiple dose therapy with propranolol or cimetidine has no effect on the pharmacokinetics of single doses of ACCUPRIL.
- The anticoagulant effect of a single dose of warfarin (measured by prothrombin time) was not significantly changed by quinapril coadministration twice-daily.
- ACCUPRIL treatment did not affect the pharmacokinetics of digoxin.
- No pharmacokinetic interaction was observed when single doses of ACCUPRIL and hydrochlorothiazide were administered concomitantly.

Carcinogenesis, Mutagenesis, Impairment of Fertility

Quinapril hydrochloride was not carcinogenic in mice or rats when given in doses up to 75 or 100 mg/kg/day (50 to 60 times the maximum human daily dose, respectively, on a mg/kg basis and 3.8 to 10 times the maximum human daily dose when based on a mg/m² basis) for 104 weeks. Female rats given the highest dose level had an increased incidence of mesenteric lymph node hemangiomas and skin/subcutaneous lipomas. Neither quinapril nor quinaprilat were mutagenic in the Ames bacterial assay with or without metabolic activation. Quinapril was also negative in the following genetic toxicology studies: *in vitro* mammalian cell point mutation, sister chromatid exchange in cultured mammalian cells, micronucleus test with mice, *in vitro chromosome* aberration with V79 cultured lung cells, and in an *in vivo* cytogenetic study with rat bone marrow. There were no adverse effects on fertility or reproduction in rats at doses up to 100 mg/kg/day (60 and 10 times the maximum daily human dose when based on mg/kg and mg/m², respectively).

Pregnancy

Pregnancy Category D: See WARNINGS, Fetal/Neonatal morbidity and mortality.

Nursing Mothers

It is not known if quinapril or its metabolites are secreted in human milk. Quinapril is secreted to a limited extent, however, in milk of lactating rats (5% or less of the plasma drug concentration was found in rat milk). Because many drugs are secreted in human milk, caution should be exercised when ACCUPRIL is given to a nursing mother.

Geriatric Use

Elderly patients exhibited increased area under the plasma concentration time curve (AUC) and peak levels for quinaprilat compared to values observed in younger patients, this appeared to relate to decreased renal function rather than to age itself. In controlled and uncontrolled studies of ACCUPRIL where 918 (21%) patients were 65 years and older, no overall differences in effectiveness or safety were observed between older and younger patients. However, greater sensitivity of some older individual patients cannot be ruled out.

Pediatric Use

The safety and effectiveness of ACCUPRIL in children have not been established.

ADVERSE REACTIONS

ACCUPRIL has been evaluated for safety in 4960 subjects and patients. Of these, 3203 patients, including 655 elderly patients, participated in controlled clinical trials. ACCUPRIL has been evaluated for long-term safety in over 1400 patients treated for 1 year or more.

Adverse experiences were usually mild and transient.

Discontinuation of therapy because of adverse events was required in 4.7% of patients treated with ACCUPRIL in placebo-controlled hypertension trials.

Adverse experiences probably or possibly related to therapy or of unknown relationship to therapy occurring in 1% or more of the 1563 patients in placebo-controlled hypertension trials who were treated with ACCUPRIL are shown below.

Adverse Events in Placebo-Controlled Trials

	ACCUPRIL (N = 1563) Incidence (Discontinuance)	Placebo (N = 579) Incidence (Discontinuance)
Headache	5.6 (0.7)	10.9 (0.7)
Dizziness	3.9 (0.8)	2.6 (0.2)
Fatigue	2.6 (0.3)	1.0
Coughing	2.0 (0.5)	0.0
Nausea/Vomiting	1.4 (0.3)	1.9 (0.2)
Abdominal Pain	1.0 (0.2)	0.7

Clinical adverse experiences probably or possibly related, or of uncertain relationship to therapy, occurring in 0.5% to 1.0% (except as noted) of the patients treated with ACCUPRIL (with or without concomitant diuretic) in controlled or uncontrolled trials (N = 4397) and less frequent, clinically significant events seen in clinical trials or post-marketing experience (the rarer events are in italics) include (listed by body system):

General: back pain, malaise

Cardiovascular: palpitation, vasodilation, tachycardia, *heart failure, hyperkalemia, myocardial infarction, cerebrovascular accident, hypertensive crisis, angina pectoris, orthostatic hypotension, cardiac rhythm disturbances*

Gastrointestinal: dry mouth or throat, constipation, *gastrointestinal hemorrhage, pancreatitis, abnormal liver function tests*

Nervous/Psychiatric: somnolence, vertigo, syncope, *nervousness, depression*

Integumentary: increased sweating, pruritus, *exfoliative dermatitis, photosensitivity reaction*

Urogenital: *acute renal failure*

Other: amblyopia, pharyngitis, sinusitis, bronchitis, *agranulocytosis, thrombocytopenia*

Angioedema: angioedema has been reported in patients receiving ACCUPRIL (0.1%). Angioedema associated with laryngeal edema may be fatal. If angioedema of the face, extremities, lips, tongue, glottis, and/or larynx occurs, treatment with ACCUPRIL should be discontinued and appropriate therapy instituted immediately. (See WARNINGS.)

Clinical Laboratory Test Findings

Hematology: (See WARNINGS)

Hyperkalemia: (See PRECAUTIONS)

Creatinine and blood urea nitrogen: Increases (>1.25 times the upper limit of normal) in serum creatinine and blood urea nitrogen were observed in 2% and 2%, respectively, of patients treated with ACCUPRIL alone. Increases are more likely to occur in patients receiving concomitant diuretic therapy than in those on ACCUPRIL alone. These increases often remit on continued therapy.

New!
ONCE-A-DAY*
ACCUPRIL®
quinapril HCl tablets

* In some patients, the antihypertensive effect may diminish toward the end of the once-daily dosing interval. In such patients, an increase in dosage or twice-daily administration may be warranted.

PARKE-DAVIS
Division of Warner-Lambert Company
Morris Plains, New Jersey 07950

PD-103-JA-7164-A2(022)

INFORMATION FOR AUTHORS

Manuscripts: Manuscripts will be accepted for consideration with the understanding that they are original contributions, have never been published or submitted elsewhere, and are submitted only to the *Rhode Island Medical Journal.*

Specifications: Manuscripts must be original typed copy (not all capitals) on 8½ × 11 inch firm typewritten paper, double-spaced throughout (including title page, text, acknowledgments, and references) with margins of at least one inch and using but one side of each page. Tables, charts, and legends should be submitted separately from the text, and referred to by number (ie, Fig. 1) within the text. Subheadings must be inserted at reasonable intervals to break the typographic monotony of the text. Pages must be numbered consecutively. Italics and boldface print are never used except as subheadings.

Abbreviations: The *Journal* attempts to avoid the use of jargon and abbreviations. All abbreviations, especially of laboratory and diagnostic procedures, must be identified in the text.

Title Page: All manuscripts must include a title page which provides the following information: (1) a concise and informative title; (2) the name of the author or authors with their highest academic degree (ie, MD, PhD); (3) a concise biographical description for each author which includes specialty, practice location, academic appointment, and primary hospital affiliation; (4) mailing address and office telephone of principal author; (5) mailing address of author responsible for correspondence or reprint requests; (6) source of support if applicable.

Illustrations: Authors are urged to use the services of professional illustrators and photographers. Drawings and charts should always be done in black ink on white paper. Clear, black and white 5 × 7 glossy photographs should be submitted, and such illustrations numbered consecutively and their positions indicated in the text. Original magnifications should be noted. Illustrations defaced by handwriting or excessive handling will not be accepted. The figure number, indication of the top, and the name of the author must be attached to the back of each illustration. Legends for illustrations should be typewritten on a single list, with the numbers corresponding to those on photographs and drawings. Recognizable photographs of patients are to be appropriately masked and must carry with them written permission for publication. Special arrangements must be made with the editors for excessive numbers of illustrations. Color plates are not acceptable.

Identification of Patients: Names, initials should not be used. Use of numbers is a preferable form of identification.

Reprints: Because of cost considerations, reprints are not provided routinely to the author(s). Reprints may be ordered separately (100 copies minimum order) and printing costs will be charged to the author(s).

Responsibility: Manuscripts are subject to editorial revisions as deemed necessary by the editors and such modifications will be undertaken so as to bring them into conformity with *Journal* style, which is in compliance with the editorial standards of the AMA. However, neither the editors, nor the publishers, nor the Rhode Island Medical Society will accept responsibility for statements made or opinions expressed by any contributor in any article or feature published in the pages of the *Journal.*

Permission: When material is reproduced from other sources, full credit must be given both to the author and publisher of these sources. Where work is reported from a governmental service or institution, clearance by the appropriate authority must accompany the manuscript.

References: To conserve space and expense, references should be limited to those essential to the subject. The editor reserves the right to reduce the number when it is deemed necessary. The references must be double-spaced and numbered as they appear consecutively in the text, with their positions clearly indicated in the text. All references must be checked to assure complete accuracy. Each journal reference must include the full name of the author(s); complete title of paper; name of publication; volume number; issue number; first and last page of paper; and date (year, month, and day as indicated). Each book reference must include the full name of author(s), editor(s), or both, with initials; title of book; edition; publisher; location; year of publication, volume (if given); and page number. If the reference is to a chapter within a book, the author of the chapter, if different than the author of the book, and the title of the chapter (if any) must be provided.

Correspondence: All correspondence relating to publication should be addressed to: Managing Editor, *Rhode Island Medical Journal,* 106 Francis Street, Providence, RI 02903.

For the many faces of mild hypertension

#1 MILD

THE MOST WIDELY USED CALCIUM ANTAGONIST AS MONOTHERAPY FOR MILD HYPERTENSION[1]*

- Effective 24-hour control[2]
- Single-agent efficacy
- Well tolerated†
- No adverse effects on total cholesterol, plasma glucose levels, renal function,‡ or serum electrolytes[3-5]

ONCE-DAILY
Calan® SR
verapamil HCl
180 mg
CAPLETS 240 mg

For the many faces of mild hypertension

*The recommended starting dose for Calan SR is 180 mg once daily. Dose titration will be required in some patients to achieve blood pressure control. A lower initial starting dosage of 120 mg/day may be warranted in some patients (eg, the elderly, patients of small stature). Dosages above 240 mg daily should be administered in divided doses. Calan SR should be administered with food.

†Constipation, which is easily managed in most patients, is the most commonly reported side effect of Calan SR.

‡Verapamil should be administered cautiously to patients with impaired renal function.

References: 1. Data on file, Searle. 2. Edmonds D, Würth JP, Baumgart P, et al. Twenty-four-hour monitoring of blood pressure during calcium antagonist therapy. In: Fleckenstein A, Laragh SH, eds. *Hypertension—the Next Decade: Verapamil in Focus*. New York, NY: Churchill Livingstone; 1987:94-100. 3. Midtbø KA. Effects of long-term verapamil therapy on serum lipids and other metabolic parameters. *Am J Cardiol*. 1990;66:131-151. 4. Fagher B, Henningsen N, Hulthén L, et al. Antihypertensive and renal effects of enalapril and slow-release verapamil in essential hypertension. *Eur J Clin Pharmacol*. 1990;39(suppl 1):S41-S43. 5. Schmieder RE, Messerli FH, Garavaglia GE, et al. Cardiovascular effects of verapamil in patients with essential hypertension. *Circulation*. 1987;75:1030-1036. 6. Midtbø K, Lauve O, Hals O. No metabolic side effects of long-term treatment with verapamil in hypertension. *Angiology*. 1988;39:1025-1029.

BRIEF SUMMARY

Contraindications: Severe LV dysfunction (see *Warnings*), hypotension (systolic pressure < 90 mm Hg) or cardiogenic shock, sick sinus syndrome (if no pacemaker is present), 2nd- or 3rd-degree AV block (if no pacemaker is present), atrial flutter/fibrillation with an accessory bypass tract (eg, WPW or LGL syndromes), hypersensitivity to verapamil.

Warnings: Verapamil should be avoided in patients with severe LV dysfunction (eg, ejection fraction < 30%) or moderate to severe symptoms of cardiac failure and in patients with any degree of ventricular dysfunction if they are receiving a beta-blocker. Control milder heart failure with optimum digitalization and/or diuretics before Calan SR is used. Verapamil may occasionally produce hypotension. Elevations of liver enzymes have been reported. Several cases have been demonstrated to be produced by verapamil. Periodic monitoring of liver function in patients on verapamil is prudent. Some patients with paroxysmal and/or chronic atrial flutter/fibrillation and an accessory AV pathway (eg, WPW or LGL syndromes) have developed an increased antegrade conduction across the accessory pathway bypassing the AV node, producing a very rapid ventricular response or ventricular fibrillation after receiving I.V. verapamil (or digitalis). Because of this risk, oral verapamil is contraindicated in such patients. AV block may occur (2nd- and 3rd-degree, 0.8%). Development of marked 1st-degree block or progression to 2nd- or 3rd-degree block requires reduction in dosage or, rarely, discontinuation and institution of appropriate therapy. Sinus bradycardia, 2nd-degree AV block, sinus arrest, pulmonary edema and/or severe hypotension were seen in some critically ill patients with hypertrophic cardiomyopathy who were treated with verapamil.

Precautions: Verapamil should be given cautiously to patients with impaired hepatic function (in severe dysfunction use about 30% of the normal dose) or impaired renal function, and patients should be monitored for abnormal prolongation of the PR interval or other signs of overdosage. Verapamil may decrease neuromuscular transmission in patients with Duchenne's muscular dystrophy and may prolong recovery from the neuromuscular blocking agent vecuronium. It may be necessary to decrease verapamil dosage in patients with attenuated neuromuscular transmission. Combined therapy with beta-adrenergic blockers and verapamil may result in additive negative effects on heart rate, atrioventricular conduction and/or cardiac contractility; there have been reports of excessive bradycardia and AV block, including complete heart block. The risks of such combined therapy may outweigh the benefits. The combination should be used only with caution and close monitoring. Decreased metoprolol and propranolol clearance may occur when either drug is administered concomitantly with verapamil. A variable effect has been seen with combined use of atenolol. Chronic verapamil treatment can increase serum digoxin levels by 50% to 75% during the first week of therapy, which can result in digitalis toxicity. In patients with hepatic cirrhosis, verapamil may reduce total body clearance and extrarenal clearance of digitoxin. The digoxin dose should be reduced when verapamil is given, and the patient carefully monitored. Verapamil will usually have an additive effect in patients receiving blood-pressure-lowering agents. Disopyramide should not be given within 48 hours before or 24 hours after verapamil administration. Concomitant use of flecainide and verapamil may have additive effects on myocardial contractility, AV conduction, and repolarization. Combined verapamil and quinidine therapy in patients with hypertrophic cardiomyopathy should be avoided, since significant hypotension may result. Concomitant use of lithium and verapamil may result in a lowering of serum lithium levels or increased sensitivity to lithium. Patients receiving both drugs must be monitored carefully. Verapamil may increase carbamazepine concentrations during combined use. Rifampin may reduce verapamil bioavailability. Phenobarbital may increase verapamil clearance. Verapamil may increase serum levels of cyclosporin. Verapamil may inhibit the clearance and increase the plasma levels of theophylline. Concomitant use of inhalation anesthetics and calcium antagonists needs careful titration to avoid excessive cardiovascular depression. Verapamil may potentiate the activity of neuromuscular blocking agents (curare-like and depolarizing); dosage reduction may be required. There was no evidence of a carcinogenic potential of verapamil administered to rats for 2 years. A study in rats did not suggest a tumorigenic potential, and verapamil was not mutagenic in the Ames test. Pregnancy Category C. There are no adequate and well-controlled studies in pregnant women. This drug should be used during pregnancy, labor, and delivery only if clearly needed. Verapamil is excreted in breast milk; therefore, nursing should be discontinued during verapamil use.

Adverse Reactions: Constipation (7.3%), dizziness (3.3%), nausea (2.7%), hypotension (2.5%), headache (2.2%), edema (1.9%), CHF, pulmonary edema (1.8%), fatigue (1.7%), dyspnea (1.4%), bradycardia HR < 50/min (1.4%), AV block: total 1°,2°,3° (1.2%), 2° and 3° (0.8%), rash (1.2%), flushing (0.6%), elevated liver enzymes, reversible non-obstructive paralytic ileus. The following reactions, reported in 1.0% or less of patients, occurred under conditions where a causal relationship is uncertain: angina pectoris, atrioventricular dissociation, chest pain, claudication, myocardial infarction, palpitations, purpura (vasculitis), syncope, diarrhea, dry mouth, gastrointestinal distress, gingival hyperplasia, ecchymosis or bruising, cerebrovascular accident, confusion, equilibrium disorders, insomnia, muscle cramps, paresthesia, psychotic symptoms, shakiness, somnolence, arthralgia and rash, exanthema, hair loss, hyperkeratosis, macules, sweating, urticaria, Stevens-Johnson syndrome, erythema multiforme, blurred vision, gynecomastia, galactorrhea/hyperprolactinemia, increased urination, spotty menstruation, impotence.

4/11/91 • P91CA6277V

© 1992 Searle

A92CA6506T

Address medical inquiries to:
G.D. Searle & Co.
Medical & Scientific Information Department
4901 Searle Parkway
Skokie, IL 60077

SEARLE

G.D. Searle & Co.
Box 5110, Chicago, IL 60680

RHODE ISLAND MEDICINE

May 1992

Volume 75, Number 5

THE FRANCIS A. COUNTWAY
LIBRARY OF MEDICINE

MAY 27 1992

02 BOSTON MA 02205-9998 05/23/92

FRANCIS A COUNTWAY LIB OF ME
EXCHANGE OFFICE
10 SHATTUCK STREET
BOSTON MA 02115

Panic Disorders

Are your investments as successful as you are?

*I*f your hard work and success have allowed you to build a portfolio of $250,000 or more, we'd like to work with you.

account administrator who will act as your personal financial advisor and you'll be backed by a team of investment managers with a history of proven investment success.

[*Professionally Managed Investments*]

Because at Citizens Bank, our Trust and Investment Management team can provide you with the exceptional service, experience, and performance that will help you get the most from your investments. You'll have an

To put us to work for you call Malcolm Starr at 456-7445. Because there's never been a better time for Citizens.

Trust and Investment Management Services

CITIZENS BANK

Citizens Trust Company/Citizens Savings Bank

RHODE ISLAND MEDICINE

Publication of the Rhode Island Medical Society

EDITORIAL STAFF

Stanley M. Aronson, MD
Editor-in-Chief

Anne M. Christner, PhD
Managing Editor

Hugo Taussig, MD
Book Review Editor

Seebert J. Goldowsky, MD
Editor-in-Chief Emeritus

John P. Sulima
Production Editor

Betsy Hunt
Advertising Manager

EDITORIAL BOARD

*Edward R. Feller, MD
Chairman

*Joseph Amaral, MD

*Stanley M. Aronson, MD

Edward M. Beiser, PhD, JD

Paul Calabresi, MD

*Richard A. Carleton, MD

Margaret Cololan, MSJ

*James P. Crowley, MD

*Peter A. Hollmann, MD

*Margaret A. Neill, MD

*Frank J. Schaberg, Jr., MD

*Fred J. Schiffman, MD

William J. Waters, Jr., PhD

*Member of Publications Committee

OFFICERS

Kathleen C. Hittner, MD
President

Robert E. Baute, MD
President-Elect

A. Robert Buonanno, MD
Secretary

Frances P. Conklin, MD
Treasurer

Richard Wong, MD
Immediate Past President

DISTRICT AND COUNTY PRESIDENTS

Fred Vohr, MD
Bristol County Medical Society

William F. Coscina, MD
Kent County Medical Society

Orest Zaklynsky, MD
Newport County Medical Society

David P. Carter, MD
Pawtucket Medical Association

James P. Crowley, MD
Providence Medical Association

Joseph R. Dotolo, MD
Washington County Medical Society

Patrick R. Levesque, MD
Woonsocket District Medical Society

Volume 75, Number 5 May 1992

TABLE OF CONTENTS

COMMENTARIES

233 Panic Disorders: Introduction
Martin B. Keller, MD

Kimberly A. Poulton

The Language of Epidemiology (XI.) Probability

CONTRIBUTIONS – PANIC DISORDERS
Guest Editor: Martin B. Keller, MD

241 **The Anxiety Disorders: An Overview**
Kerrin White, MD

247 **Neurobiological Aspects of Panic Disorder**
Gary B. Kaplan, MD

253 **Treatment of Panic Disorder**
Paul E. Alexander, MD

262 **Panic Disorder: A Clinical Perspective on Acute Treatment and Future Research Needs**
Alan Gordon, MD

265 **Medical Aspects of Panic Disorder**
Richard J. Goldberg, MD

273 **Panic Disorder in Children and Adolescents**
Greta Francis, PhD
Douglas R. Robbins, MD
W.L. Grapentine, MD

277 **Comorbidity of Panic Disorder and Substance Use Disorders**
Timothy I. Mueller, MD
Robert M. Swift, MD, PhD

COLUMNS

237 LETTERS TO THE EDITOR

282 HEALTH BY NUMBERS
Workplace Smoking Policies of Rhode Island Employers

285 THE RHODE ISLAND MEDICAL JOURNAL HERITAGE

Cover: A self-portrait, in ink, of Albrecht Dürer when he was 20 years old. Dürer was born in Nuremberg, Germany, of Hungarian origin, in 1471 and died in 1528.

Rhode Island Medicine is owned and published monthly by the Rhode Island Medical Society, 106 Francis Street, Providence, Rhode Island 02903, Ph: 401-331-3207. Single copies $2.00 — Subscriptions $20.00 per year (members of the Rhode Island Medical Society — $5.00 annually). Published articles represent opinions of the authors and do not necessarily reflect the official policy of the Rhode Island Medical Society unless clearly specified. Advertisements do not imply sponsorship or endorsement by the Rhode Island Medical Society. Second class postage paid at Providence, Rhode Island. ISSN 1061-222X. POSTMASTER: Send address changes to RHODE ISLAND MEDICINE, 106 Francis Street, Providence, RI 02903. National Advertising Bureau: State Medical Journal Advertising Bureau, Inc., 711 South Blvd., Oak Park, Illinois 60302. Phone 708-383-8800.

You treated little Johnny for measles in kindergarten, chicken pox in 3rd grade, mono in high school.

But what can you do for his HIV today?

People with HIV are special patients with specific needs. That's why it helps to have experience with HIV when treating an infected patient–the kind of experience doctors find at Clinical Partners.

Clinical Partners is a group of healthcare professionals dedicated to helping patients live with HIV. We are alone in the complete array of services we provide to physicians, employers and insurers of those living with HIV. Our early intervention averts costly hospital stays, while increasing patient care and support.

Operating successfully in Boston, New York and Los Angeles, Clinical Partners is pleased to announce the first anniversary of our Providence office, under the expert guidance of Linda Durand NP, RNC and Deborah Matson CISW, MSW.

We want Rhode Island physicians to know Clinical Partners is here to help, and here to stay. As the patient's primary physician, you can benefit from our knowledge and experience, which is available to help you treat HIV infection and AIDS.

To find out how Clinical Partners can be your partner in treating HIV patients, call our Providence office today at 454-8880 or 1-800-285-8880.

ClinicalPartners

Helping people make choices about HIV.

COMMENTARIES

Panic Disorders: Introduction

In September 1991, the National Institutes of Health with the National Institute of Mental Health (NIMH) organized a panel of experts in psychology, psychiatry, cardiology, internal medicine, and methodology to discuss panic disorder. The consensus conference addressed important questions including natural history, diagnosis, course, treatment efficacy and side effects, and implications for future research. This significant meeting resulted in a statement that begins, "Panic disorder with and without agoraphobia is a debilitating condition that will afflict as many as 1 out of every 75 people in this country and worldwide during their lifetime." Its main conclusions are that there is a growing body of knowledge about panic disorder and that there are medications and psychosocial treatments that are efficacious short-term therapies. There are, however, significant public health problems with underrecognition and undertreatment. Moreover, there is a need to develop long-term maintenance and preventive treatment strategies.

Anxiety disorders are among the most common and earliest described psychiatric disorders, with a history of documentation in medical literature going back to the time of Hippocrates. Clinical descriptions have appeared for several centuries. In the late 1800s Westphal (1872) wrote about agoraphobia and Beard (1880) defined neurasthenia. In 1894 Freud published a paper proposing the separation of anxiety neurosis from neurasthenia. That paper distinguished two distinct types of anxiety that are now called panic attacks and generalized anxiety. Freud also found a high comorbidity with depression, and he noted frequency of avoidance behavior and social disability. The symptoms of anxiety – palpitations, dizziness, chest pains, shortness of breath, and others – typically lead physicians and researchers to postulate cardiac origins for this cluster of illnesses.

Panic symptoms often are similar to those of many medical illnesses (asthma, cardiac arrhythmias, coronary artery disease, hyperthyroidism, and temporal lobe epilepsy, among others), and therefore, patients often are misdiagnosed as having nonpsychiatric medical conditions. A study published in the *American Journal of Psychiatry* concluded that a diagnosis of panic disorder should be considered in all patients being seen medically for atypical or non-anginal chest pain (1987).

Even today physicians commonly fail to recognize panic disorder as a possible cause of chest pain in their patients (Beitman, 1989). According to this investigator, 34% of a sample of 94 cardiology patients actually suffered from panic disorder rather than coronary heart disease.

It is because of this confusion in diagnosis that the anxiety disorders have received a number of labels over the years: anxiety neurosis, cardiac neurosis, irritable heart, soldier's heart, nervous exhaustion, vasomotor neurosis, and circulatory neurasthenia, among others. In 1980, a major change occurred in the criteria and classification of anxiety disorders leading to the nomenclature currently in use in the *DSM-III-R* as Panic Disorder, with and without Agoraphobia; Agoraphobia without Panic Disorder; Social Phobia; Simple Phobia; Obsessive-Compulsive Disorder; Post-Traumatic Stress Disorder; Generalized Anxiety Disorder; and Anxiety Disorder, Not Otherwise Specified.

Panic disorder is characterized by the occurrence of severe panic attacks that have no apparent precipitant. For a patient to receive a diagnosis of panic disorder, he or she must experience four such panic attacks in a four-week period. Panic disorder also is defined as the occurrence of one or more panic attacks taking place in one month, followed by the persistent fear of having another attack.

According to Lewis Judd, MD, past director of the National Institute of Mental Health and now chairman of the Department of Psychiatry at the University of California (San Diego), anxiety disorders are among the nation's most common forms of mental illness. Panic disorder, which affects more than 1.5 million Americans, is one of the most crippling of the anxiety disorders. Typically, people with anxiety disorders see up to 10 clinicians before they are diagnosed correctly.

In November 1991, the NIMH launched the Panic Disorder Prevention and Public Education Program, a campaign to increase awareness in the general public and health care practitioners about panic disorder. The project will use printed and audiovisual materials for the lay public and medical professionals about the symptoms and treatment of panic disorder. The Institute plans to work closely with

professional societies, mental health voluntary organizations, and the media to ensure widespread distribution of the information. The goal of this project is to increase the probability that people suffering from panic disorder are diagnosed and treated accurately.

The earliest substantial work on panic and other anxiety disorders was published more than 40 years ago by Paul Dudley White, MD (Wheeler et al, 1950), a cardiologist, and three of his colleagues at the Massachusetts General Hospital in Boston. White's study was a 20-year follow-up of 173 patients who were diagnosed with "neurocirculatory asthenia." The symptoms of the disorder were breathlessness, palpitation, chest pain, nervousness, fatigue, headache, dizziness, apprehension, and trembling; the clinical signs included tachycardia, tachypnea, tremor of fingers, and overactive deep tendon reflexes. These signs and symptoms closely mirror what today would be classified as panic disorder.

Although the Wheeler et al study was not a randomized clinical trial, the treatments received by the subjects were recorded and included psychotherapy, psychoanalysis, ergotamine tartrate, and adrenal denervation. Given that these treatments would be regarded today as ineffective for panic disorder, White's study provides valuable insight into the naturalistic course of untreated illness.

The findings indicated that "neurocirculatory asthenia" was a chronic illness. Over the course of 20 years, 12% of the original patients had recovered from the illness; 35% continued to have symptoms but no significant disability; 38% experienced symptoms and mild disability; and 15% still experienced moderate to severe disability.

It is significant that this early study emerged from the practice of a cardiologist, since one of the main ways that patients with panic disorder presented unrecognized was in the emergency rooms of general hospitals with symptoms mimicking cardiovascular disease. In fact, early researchers frequently attributed cardiac origins to panic symptoms. Early labels for the disorder – such as cardiac neurosis, irritable heart, soldier's heart, nervous exhaustion and vasomotor neurosis – reflected this belief.

Marks and Lader (1973) reviewed six retrospective studies of the course of panic disorder conducted between 1950 and 1966 (the Wheeler et al study, just discussed, was included in the Marks and Lader review). These studies also may be considered naturalistic, since the treatments received by the subjects currently are considered ineffective for panic disorder: reassurance and sedatives; psychotherapy with a mean of seven sessions; and "support" (Eitinger, 1955; Ernst et al, 1959; Greer and Cawley, 1966; Miles, 1966; Blair et al, 1957).

The follow-up period of these studies ranged from 1 year (Blair et al, 1957) to 20 years (Wheeler et al, 1950), and a total of 300 patients with anxiety disorders were surveyed. On average 41% to 50% of the patients were recovered or improved at the end of follow-up across the six studies (Marks and Lader, 1973). However, more than half the patients experienced little or no improvement, even over long periods of follow-up.

Although the studies reviewed by Marks and Lader were retrospective and did not use structured clinical interviews to gather baseline and follow-up information, they still suggest that anxiety disorders, including panic disorder, follow a chronic and recurrent course not unlike that found in depression.

Studies done during the 1970s and 1980s also reflect high rates of at least moderate symptomatology after follow-up periods ranging from three to eight years. For example, Noyes et al (1980) reported that 88% of 112 patients with anxiety disorders continued to experience either mild (40%) or moderate (48%) symptoms after four- to nine-year follow-ups. Noyes and Clancy (1976) found that 84% of 57 patients had mild (51%) and moderate (33%) symptoms after three- to eight-year follow-ups. The treatment received by the patients in these studies was not specified.

However, even in two studies that report treatment received by the anxiety patients, relatively high rates of chronicity are reported. Nagy (1989), in a study of 60 patients with anxiety disorders who received treatment with alprazolam (1.2±0.2 mg per day) and behavioral therapy, reported that 38% of the patients experienced mild symptoms after one to four year follow-ups, and 18% continued to experience at least moderate symptoms. Noyes (1989) reported continued mild or moderate symptoms in 38% and 50% respectively, of 107 anxiety patients receiving 150 mg to 350 mg per day of imipramine over one- to four-year follow-ups.

A number of researchers have conducted studies on the occurrence of panic disorder in the general public. The Epidemiological Catchment Area Study found lifetime estimates of panic disorder ranging from 0.6% to 1.2% in men, and 1.6% to 2.1% in women (Weissman, 1987). Panic disorder tends to be more common in women with a 2:1 female to male ratio.

The Harvard/Brown Anxiety Disorders Research Project (HARP), a prospective, naturalistic, longitudinal, multi-center study of patients with anxiety disorder, has entered 725 subjects from 12 different sites in the northeastern and central United States (Keller, 1990). The specific aims of the HARP study are to: prospectively observe and describe the naturalistic course of the anxiety disorders, including recovery from the index episode and relapse; describe the clinical characteristics of subjects with these diagnoses; evaluate the consistency of longitudinal diagnostic assessments of panic-related disorders using the Longitudinal Interval Follow-Up Evaluation (LIFE); identify factors that predict clinical course and psychosocial function; and describe and assess the effect of treatment as a mediating variable affecting outcome in naturalistic research on anxiety disorders.

This study of the clinical and treatment characteristics will provide an understanding of the patterns of course over time of panic-related disorders,

particularly in comparison to other psychiatric disorders. It also will allow us to predict recurrence of illness, change of diagnosis, treatment status, suicide, death and major psychosocial outcomes.

This program is a long-term study of the course of illness in patients with present or past diagnosis of either panic disorder or agoraphobia. The HARP study is a naturalistic study which means that no attempt has been made to alter or influence the treatment received by the subjects. All treatment decisions were made by the subject and his or her personal physician.

The preliminary findings from the HARP study serve to emphasize both the chronicity of panic disorder and its frequent comorbidity with other anxiety disorders as well as with depression. The overall 28% comorbidity of depression in the panic subjects suggests that clinicians treating patients for this disorder should be aware of and vigorously treat the depression as well as the panic disorder. This is especially true given that numerous studies have documented the chronicity of the depressive disorders.

HARP study data analyzed thus far indicate that patients with panic disorder have high levels of chronicity and relapse, despite the fact that almost all subjects received some type of somatotherapy during the follow-up period. It has been alarming to see that the intensity of treatment is far below levels shown to be effective in randomized clinical trials. In particular, the presence of comorbid depression predicts severe psychopathology and considerable psychosocial impairment, as reflected in measures of subjects' work, home, and leisure functioning. It is possible that clinicians, by failing to diagnose comorbid depressive disorders, treat these patients with low or no antidepressant somatotherapy. Further follow-up is essential to learn about the long-term course of panic and other anxiety disorders.

This edition includes an overview from Kerrin White, MD, of the anxiety disorders with specific clinical descriptions of each of eight diagnoses. Gary Kaplan, MD, presents a thorough article on the pathophysiology of panic disorder. There are two articles that address the issues of treatment. The article by Paul Alexander, MD, serves as a comprehensive review of the literature, and the article by Alan Gordon, MD, is from a clinical perspective and includes a clinical case presentation. The article by Richard Goldberg, MD, discusses the medical aspects of panic disorder including a number of medical conditions that manifest similar symptoms and, therefore, complicate diagnosis. In their article, Greta Francis, PhD, Douglas Robbins, MD, and WL Grapetine, MD, explore panic disorder in children and adolescents including course and treatment. Finally, Timothy Mueller, MD, and Robert Swift, MD, PhD, discuss the comorbidity of panic disorder and substance abuse disorders, including a case example.

I thank the authors who contributed to this issue of *Rhode Island Medicine*. This collection of work represents the strong, comprehensive diversity of interest and the high quality of work found in the Rhode Island medical community. All contributing authors are on the faculty at Brown University Medical School in the Department of Psychiatry and Human Behavior. I am deeply appreciative to them for the scholarship of their manuscripts and for their excellence in clinical care of patients, teaching of medical students, and research. I am also deeply appreciative to Dr Mueller for helping to integrate and cross-reference each of the articles in this edition and to Ms Liz Prager for her superb clarity as an editorial assistant.

Dr Keller will provide a bibliography to this editorial for those wishing a listing. Contact: Martin B. Keller, MD, Professor and Chairman, Department of Psychiatry and Human Behavior, Brown Medical School, Butler Hospital, 345 Blackstone Blvd, Providence, RI 02906. – Ed.

Martin B. Keller, MD

Kimberly A. Poulton

For the past half decade, *Rhode Island Medicine* has been managed by Kimberly Allyn Poulton, a person of discernment, good taste, profound respect for the English language and commitment to the Medical Society of Rhode Island. During this interval, the technical and business affairs of the Society's monthly publication have been directed with flawless efficiency and dispatch. The burdens of the editor and the editorial board were lightened immeasurably by Ms Poulton's unflagging skills and dedication. The April 1992 issue will be the last one with Ms Poulton as managing editor. We will miss her deeply, and we join in wishing her much success and fulfillment in her new post at Blue Cross/ Blue Shield of Rhode Island.

The Editorial Board
Rhode Island Medicine

The Language of Epidemiology (XI.) Probability

A rate of 37 per 100,000 population is precisely the same whether it is recorded in Central Falls or Niagara Falls. When narrative prose replaces numeric expressions, however, it may add warmth and color to the message, but inevitably it will forsake the exactness that we demand of mathematics.

A language such as English, abundantly rich in words, can still afford to dedicate a few of them to duty in the trenches of numeric science, assigning to them narrowly precise and unambiguous meanings. We strengthen our capacity to communicate in the sciences if we zealously guard the semantic purity of such selected words.

Take the word *probability*. Narrowly defined, it signifies the likelihood of a future occurrence, expressed by the ratio of the number of actual occurrences to that of possible occurrences. More simply stated, it is a predictive inference, in quantitative terms, of some future event based upon

some past experience. Probability thus becomes a fundamental scientific instrument that declares that happenings in nature are subject not only to description but also prediction. The process of assigning a probability value begins with the question: Given the current circumstances, what are all the outcome probabilities, no matter how remote each might be? Having defined these future outcomes (sometimes called the sample space) we then recruit our prior observations in circumstances closely similar to the present to guide us in delegating some numeric likelihood – some probability – to each of the possible outcomes. In things as simple as a coin toss, we assign 0.5 value to heads, 0.5 to tails and 1.0 to either head or tail (assuming, of course, no coins falling on their edges). In settings more complex, we ask, what has preceded or been associated with what in our professional memories? If, blind-folded on Broadway in Providence we heard hoofbeats, we might hazard a guess – a prediction – that there are horses approaching, not zebras.

In a medical setting we distill past experience of similar nature, and then translate them into a statement couched in numeric terms. We call it either prognosis or risk. To preserve a sense of humanity, with prognosis, the numeric component is often hidden behind indeterminate words such as grave, or clouded, or desperate.

In what way does prognosis differ from probability or risk? Probability indicates the numeric likelihood of an event occurring in the future. The event has not yet happened – but it may. Prognosis is a much more shadowed word. It, too, is a probability, but of the ultimate outcome of a somber event, customarily a disease, which has already appeared. And not just any disease, but particularly those with some chance of death as the outcome. Both risk and prognosis are also probabilities, but we talk of the risk of lung cancer, based upon the presence or absence of certain reliable precursor factors (eg, history of smoking) *before* the disease has materialized. But once the disease is clinically present we then talk no longer of risk but of prognosis.

Probability, the descriptor of both risk and prognosis, operates between the limits of 0.0 and 1.0. Probability, aside from this rigorous usage, carries other meanings in everyday speech. It may even carry an unstated numeric message. "Will it snow tomorrow?" One response might be, "Possibly" (suggesting that snow is no more than one of many reasonable weather outcomes for tomorrow). If, on the other hand, the answer is, "Probably" it suggests a higher likelihood of a near future snowfall. In the minds of some, "probably" signifies "a better than even chance."

Numericists insist that probability (and its adverbial term, probably) be strictly neutral, applying to all outcomes no matter how remote or likely. Where, then, did the current meaning of probability arise (ie, suggesting high likelihood)? The Latin ancestor for probability is *probare*, to verify. The current verb, *to probe*, preserves much of this earlier meaning. Placing someone on *probation* is an act of testing, of evaluating, of *probing* the person's credentials. A *probate court* is a place where the authenticity of wills are established. And, of course, one whose value has been proven is a person of *probity*. The word, *probable*, in theologic discourse (eg, a probable statement) refers more to the probity of the commentator and not necessarily to the merit of his commentary. By inference, though, the probity of the speaker has spread to his issuances and probable came to mean near certainty. *Probabilism*, on the other hand, focuses on the lack of ultimate certainties in life and defines a theologic doctrine that states that certainty is impossible and therefore in instances of moral doubt, one may follow a soundly *probable* opinion. A *problem* is something which requires probing. And *problematic* brings the meaning back to an earlier sense, namely, something which is unsettled or indeterminate.

Probability, as used in medicine, is neutral, unbiased and indifferent to import. For example, a 0.06 probability of muscular strain carries the same predictive strength as a 0.06 probability of muscular dystrophy – although there are vast distinctions in prognosis and in the feelings of those involved.

Words are beguiling and malleable, but numbers are sturdy and resistive to change. "Probable impossibilities," said Aristotle, "are to be preferred to improbable possibilities." A cleverly delightful invention with words, but if we ignore the adjectives, his sentence reduces to a bewildering, "impossibilities are preferred to possibilities." Meaning and clarity, especially in the sciences, should take precedence over cleverness.

Stanley M. Aronson, MD

1,000 SQ. FT.

Recently completely renovated 1st floor

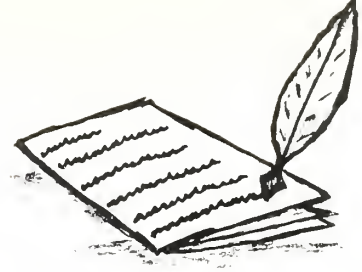
Large office space includes
3 examining rooms, consultation room, reception area.

AVAILABLE NOW

Medical Building • 1524 Atwood Avenue • Johnston

CALL 521-6085

EDITOR'S MAILBOX



To the Editor:

In the February 1991 issue, *Rhode Island Medicine* noted that at the first demonstration of anesthesia at the Massachusetts General Hospital, "no one had bothered to time the induction."

Not only did no one record the details of the administration of this first anesthesia but few details of any anesthesia were recorded in patient records for several generations. It seems incredible in our age of zealous documentation that for 50 years after the discovery of anesthesia there was no systematic recording of the administration of anesthesia. Perhaps the standard of medical record-keeping was less demanding, and perhaps there were fewer litigious malpractice attorneys preying upon physicians with less than voluminous documentation.

The first detailed and systematic anesthesia records appear to have been kept at the same institution where anesthesia was first demonstrated. The records were kept in 1895-1896 by two young house officers, EA Codman and Harvey Cushing.[1] Codman had come to the hospital eight months before Cushing and started to keep the records at the suggestion of FB Harrington, MD. Harrington was a young attending surgeon at MGH and later served as medical advisor to the corporation of the Peter Bent Brigham Hospital at the time Harvey Cushing accepted his position there.[2]

A friendly competition emerged between Codman and Cushing to see "who could learn to give the best anesthesia." Cushing did not recall who won this wager. He did recall, however, that the keeping of detailed records improved the quality of the anesthesia. These early "ether charts" contained measurements of pulse and respiration and a short narrative description of the anesthesia and complications. Blood presssure measurements were not used clinically until after 1900.

History often teaches or reinforces a lesson, and in this case, two lessons. First, we should be reminded that accurate and detailed medical records are not just a burden imposed by administrators and lawyers but are reflections of careful and attentive care given to the patient. Keeping accurate records stimulates better care. Second, this episode of medical history reminds us again that significant contributions to the body of medical knowledge and the quality of medical care can be and often are made by persons early in their medical careers (medical students and house officers).

Herbert Rakatansky, MD
Clinical Professor of Medicine
Brown University School of Medicine

References

1 Beecher HK. The first anesthesia records. *Surg Gynecol Obstet.* 71:689-693, 1940.
2 Fulton JF, *Harvey Cushing. A Biography.* Springfield, Ill: C Thomas; 1946.

To the Editor:

You may well imagine my pleasure when I read that *Rhode Island Medicine* was going to discuss the relevance and significance of the Hippocratic Oath. No matter that I was not one of the invited guests. I have always had a love affair with those words and have long believed they are as sacred as the Ten Commandments, Declaration of Independence or the Gettysburg Address.

I had heard that there were medical students who wanted to make some changes. Why would anyone want to change something more than 2000 years old and especially a document they have not as yet had a chance to live with?

The first sentence of the Oath describes our binding heritage. For the longest time, this country described itself as a "melting pot" and believed in creating a homogeneous society. This concept gradually has given way to a country with many cultures each contributing to our heritage, and it is this persisting heterogeneity that makes us strong. Physicians are now important contributors to this societal strength by the continuing emphasis we place on moral and ethical conduct.

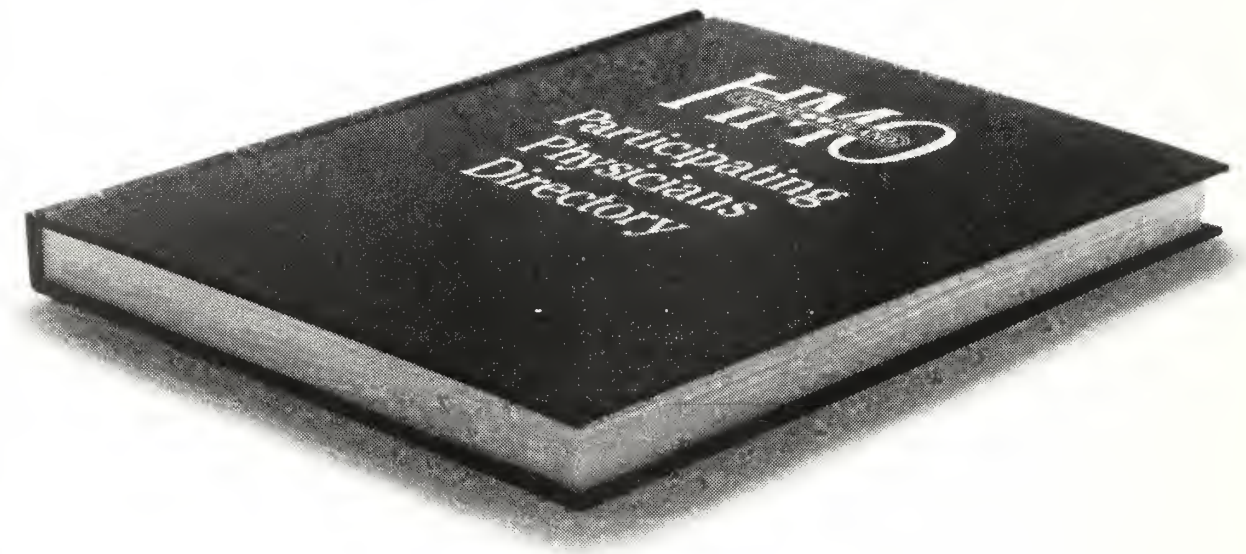
My teacher in modern context is the medical school, and I do think of my many teachers as "parents"; I do contribute to my medical school, and I would teach students my art if they so desire.

Hippocrates understood that medicine was an imprecise science. What manual dexterity is to a pianist, the textbook is to a physician. Interpretation and explanation of disease, however, are more complex processes requring an understanding of human nature, a carefulness of expression, insightful behavior, and a sensitivity to human need. "He" would administer no deleterious drug, administer no poison, cause no abortion, and respect confidentiality. Implied in this physician precept is an interpersonal relationship – that physician and that patient – resulting in the assumption of personal responsibility. The physician's major concern is to listen carefully to what the patient does and does not say.

Hippocrates, how could you have seen so clearly more than 2000 years ago! Your words are unalterable simply because they reflect on the human condition. I shall read them frequently as they are pleasing to the ear and a constant reminder of the greatness that is medicine.

Robert D. Corwin, MD
Providence, Rhode Island

This book has a happy ending.



And a happy beginning. And a happy middle.

That's no fiction. It's because we re-wrote the book on provider relations. With higher office visit allowances than other major plans. And with quick, easy access to both our Medical Director and Provider Relations staff.

But while we could cover all the reasons we're sure you'd like HMO Rhode Island, we think the best way to judge this book is to hear about it from our Primary Care Physicians and Specialists, themselves.

So ask your colleagues for the real story. Then call Physician Recruitment Manager, Carin Cookman, at (401)274-6674, or 1-800-528-4141. Or take her call when it comes.

HMO RHODE ISLAND

The Ultimate Health Maintenance Organization.

IS YOUR FINANCIAL PROGNOSIS AS BRIGHT AS IT SHOULD BE?

RIMS Insurance Brokerage Corporation (IBC) introduces complete Life Insurance and Financial Planning services. Now, the firm that provides outstanding malpractice insurance programs and workers' compensation coverage, introduces life insurance and investment services designed specifically for the health care professional.

Insuring over one third of all licensed physicians in Rhode Island, IBC is known for quick and informed service. We have programs customized for all stages of a physician's practice — from the beginning practitioner to the practitioner nearing retirement.

And now — the IBC is your one-stop resource for a complete selection of life, health, disability and investment products. Take advantage of this new path to financial security and ensure that your long-term financial prognosis is every bit as bright as it should be. **For a free financial check-up, call IBC at 272-1050.**

RIMS Insurance Brokerage Corporation

One Hayes Street • Providence, Rhode Island 02908

Phone (401) 272-1050 • Fax (401) 272-1051 • RI Toll Free 800-559-6711

NURSING PLACEMENT
HOME CARE INC.

"The 1st Choice in Certified Home Health Agencies"

We Are Proud To Announce:

NURSING PLACEMENT HOME CARE, INC.,
a **MEDICARE** and **MEDICAID CERTIFIED AGENCY.**

NPHC, the only letters that define Quality and Dependable Home Health Care in RI. Your patients deserve a choice and **NPHC** can offer them that – with a complete range of care options from Home Health Aides to Registered Nurses and all therapies.

We have provided your hospitals and private patients with quality care for 15 years and are now certified to serve all homebound patients in Rhode Island.

- RN assessments
- 24 hr. supervision
- RN
- HHA
- PT
- OT
- Speech
- MSW
- IV Therapy
- Pediatrics

"For Home Care You Can Rely On"

NPHC

Please call 453-4474
1-800-287-2940

Anxiety Disorders: An Overview

Kerrin White, MD

As a group, anxiety disorders are the most prevalent class of mental disorders. Over the course of a lifetime, 15% of the population experience one or another anxiety disorder.

The anxiety disorders are a group of eight defined syndromes in which the symptoms of anxiety and avoidance play prominent roles. They are:

1. Panic disorder with agoraphobia
2. Panic disorder without agoraphobia
3. Agoraphobia without history of panic
4. Social phobia
5. Simple phobia
6. Obsessive-compulsive disorder
7. Posttraumatic stress disorder
8. Generalized anxiety disorder

This, at least, is the current American version, represented by the *Diagnostic and Statistical Manual of Mental Disorders, Third Edition-Revised* (*DSM-III-R*).[1] For this overview, we are talking in terms of *DSM-III-R*; but those working on its next revision (*DSM-IV*) have considered adding new diagnoses and removing others.[2]

The first two diagnoses represent variants of panic disorder, distinguished on the basis of whether agoraphobia coexists. The hallmark of panic disorder is unexpected, acute attacks of anxiety with physical symptoms of autonomic arousal (rapid heartbeat, sweating, etc.), while that of agoraphobia is fear and avoidance of situations where escaping or getting help would be a problem, such as driving or going out alone.

The next three diagnoses listed represent different types of phobias distinguished by what provokes fear and avoidance: situations problematic for escape or help (agoraphobia), situations of public scrutiny (social phobia) or, more specific, threatening situations such as heights or snakes (simple phobia).

The next two diagnoses – obsessive compulsive disorder (typified by compulsive cleaners and checkers) and posttraumatic stress disorder (represented by the emotional after effects in catastrophe survivors) – are quite distinct, perhaps enough to warrant groupings of their own. Generalized anxiety disorder is a condition of chronic and diffuse anxiety and worry. There is also an undefined category for "Anxiety Disorder Not Otherwise Specified" for atypical syndrome.

Do the Anxiety Disorders Really Belong Together?

One legitimately may question whether the eight main anxiety disorders have more in common with each other than with other psychiatric diagnoses. Certainly, they all involve major elements of anxiety but so may many other disorders including depression, delirium, schizophrenia, and numerous medical illnesses. With anxiety there usually comes physical symptoms of autonomic overarousal that along with avoidance of anxiety-provoking situations, are often prominent but by no means confined to the anxiety disorders.

As a group, anxiety disorders are the most prevalent class of mental disorders. During a lifetime, 15% of

ABBREVIATIONS USED:

DSM-III-R: Diagnostic and Statistical Manual of the American Psychiatric Association, Third Edition, Revised
DSM-IV: Diagnostic and Statistical Manual of the American Psychiatric Association, Fourth Edition
GAD: Generalized Anxiety Disorder
OCD: Obsessive-Compulsive Disorder
PTSD: Posttraumatic Stress Disorder

Kerrin White, MD, is Associate Professor of Psychiatry and Human Behavior, Brown University, Providence, Rhode Island.

the population experience an anxiety disorder.[3] Much of this high prevalence is accounted for by the simple phobias, which may represent relatively "minor" problems for some people who can avoid whatever makes them most anxious without much inconvenience. However, even the more "major" syndromes carry lifetime risks in the range of 1% to 3%. Though these lifetime risks pale before the ubiquity of some medical illnesses like upper respiratory infections, they gain significance from the fact that all anxiety disorders are chronic conditions that lead to substantial impairment in functioning and quality of life. Thus, their one-month prevalence rates approximate half their lifetime risks. They affect women more often than men, but this should not obscure the fact that they affect many men as well.

Certainly everybody gets anxious from time to time, but the anxiety disorders represent more than "normal" anxiety. They clearly impair the quality of life.[4] Besides causing emotional and physical distress, they can limit freedom of movement and behavior, create interpersonal and financial dependence, and foster marital conflicts. They can lead to depression and sometimes suicidal tendencies. They contribute to drug and alcohol abuse.[5] They can lead to unnecessary, expensive, and even dangerous medical tests and interventions. There is also an associated increase in mortality.[6] Specific disorders like panic disorder may increase the risk of medical illnesses like ischemic cardiac disease and strokes.[7] To make the diagnoses, *DSM-III-R* requires certain levels of symptomatology (such as frequency of panic attacks) that may actually be set too high. There is evidence, for example, that people with panic attacks short of diagnosable panic disorder (perhaps 9% of the population) also suffer from measurably increased impairment. So for most sufferers, the anxiety disorders are not the trivial matters they often have been misconstrued to be.

All these disorders appear treatable. Symptoms can be reduced by various medications and psychological treatments such as behavior therapy. Many respond to what we call "antianxiety" medications, but other drugs, such as antidepressants, can be even more helpful. Though often not curative, these treatments offer symptomatic relief and functional improvement comparable to many valued treatments for physical illnesses.

Though there is reason for ongoing debate as to whether the eight anxiety disorder syndromes all belong in the same grouping, there is general agreement as to the integrity of specific syndromes. Panic disorder, for example, has gained the status of a prototype and is the focus of this special issue of *Rhode Island Medicine*.

Panic Disorder

Although the term "panic disorder" only recently gained diagnostic currency, the syndrome itself has been recognized under various names for many years. A landmark study[8] published four decades ago concerning 173 patients with cardiac complaints but (after evaluation by Paul Dudley White, MD) no evidence of organic cardiac pathology termed such a syndrome "neurocirculatory asthenia." Like panic disorder, it involved many physical symptoms of excessive arousal – breathlessness, palpitations, chest pain, dizziness, trembling, etc. On follow-up more than two decades later, the condition persisted and was a cause of disability in half the cases.

The hallmark of panic disorder is unexpected, acute attacks of anxiety with physical symptoms of autonomic arousal (rapid heart beat, sweating, etc.)

Typically, symptoms often begin unexpectedly without obvious cause. Along with anxiety, physical symptoms begin suddenly and increase rapidly to a peak within minutes of onset. There is sometimes a sense of having a heart attack or stroke associated with a fear of dying. The person may rush to an emergency room. Within an hour or two it has usually subsided, often leaving behind the persisting dread of having another. This may lead to avoidance of the situation in which the attack originally occurred, even though causally irrelevant. Anticipation of future attacks may lead to avoidance of situations – such as crowded stores, going out alone, or driving – where it would be especially problematic to escape, get help, or be incapacitated in case of an attack. This is the typical picture of panic disorder with agoraphobia, which, in its extreme form, may leave a person housebound or unable to go anywhere without a companion to lend a sense of security.

A diagnosis of panic disorder requires a certain minimum frequency of attacks (ie, at least once a week for a month) or persistence for at least a month of "dread" after a single attack. Also, attacks used in making the diagnosis must have at least 4 of 13 largely physical symptoms of overarousal that occur together. Attacks with fewer symptoms nevertheless are recognized as "limited symptom attacks," and it is possible that some forms may present with a single predominant symptom (eg, chest pain). Individuals with panic disorder are susceptible to experimental provocation of these attacks by physical factors such as lactate infusion and natural provocation by factors such as caffeine or cocaine use, but the attack on which the diagnosis is made cannot have arisen from such "organic" causes. Similarly, many panic attacks predictably may be associated with stressful situations but not those used to make the diagnosis. In other words, the diagnosis of panic disorder requires that the individual be susceptible enough to develop a certain frequency or marked intensity of panic on his or her own ("spontaneous" attacks), which may then occur as well in response to many physical and psychological stressors.

Panic disorder typically starts in adolescence or young adulthood but can begin in childhood or old age. (Francis *et al* discuss the major features of the less well understood adolescent panic disorder.) It often starts

during a particularly stressful period of a person's life (something different from the individual attack being precipitated by a specific stressor). It develops more frequently in people with other preexisting psychiatric problems, such as depression or substance abuse, but may arise in an emotionally healthy person. Like many psychiatric disorders, it runs in families in an apparently hereditary pattern where risk is proportional to the genetic closeness of an affected relative. The lifetime risk of panic disorder is notably constant across different geographic areas at 1.5%.

Although symptoms often improve over the course of years, and occasionally remit completely with many patients subsequently relapsing, the general tendency is for persistence of some symptoms, at least intermittently, over the course of many years. Results of studies examining course have varied considerably. Shorter-term, controlled treatment studies present more optimistic results than longer-term naturalistic studies. Perhaps half to three-quarters of patients remain chronically ill for extended periods of years (though they may experience significant symptom reduction during that time). Nevertheless, compared to the great chronicity of all the anxiety disorders, panic disorder may be the least chronic and most variable over time.

Individuals with panic disorder are susceptible to experimental provocation of these attacks by factors such as lactate infusion and natural provocation by factors such as caffeine or cocaine use . . .

As described above, agoraphobia is a common, perhaps even a usual complication of panic disorder. When present, it augurs more impairment and poorer prognosis; when treated, panic attacks often improve before agoraphobic avoidance. Depression and substance abuse are other common complications that also worsen the clinical picture and prognosis. Generalized anxiety disorder (GAD) – a pattern of less intense but more persistent anxiety symptoms than panic – often coexists with panic disorder. It is not unusual to see an individual suffering from panic disorder, another anxiety disorder like GAD, an affective disorder like major depression, in combination with a substance abuse disorder like alcoholism. Each may be amenable to its own treatment, even overlap in treatment with the others, yet still make management of the other disorders more difficult. And when several such disorders converge on an unfortunate individual early in life and persist for many years, it is not surprising to find that person developing exaggerated traits of dependency, shyness, etc to constitute a "personality disorder" as well.

Agoraphobia Without Panic Disorder

The fact that the earlier diagnostic system of *DSM-III* referred to "agoraphobia with or without panic," while the *DSM-III-R* reverses this to read "panic disorder with and without agoraphobia," reflects the more recent view of agoraphobia as largely a complication of panic. There are at least a few, perhaps many, agoraphobics who have no history of panic disorder but who may have had limited symptom attacks as a basis for their agoraphobic avoidance. As in panic disorder with agoraphobia, the basic fear is of situations where escape would be difficult or help unavailable if needed.

Social phobia is sometimes confused with agoraphobia, since sufferers from both may avoid public places, but there the fear is not inability to escape or get help but of being scrutinized by others or embarrassed and humiliated in front of them.

Although social phobia seems about as common as most of the other anxiety disorders, it has had less attention than most.[9] Even as anxiety disorders go, social phobia is one of the most chronic. Nevertheless, there is evidence that both pharmacotherapy (such as beta-blockers) and behavior therapy (such as systematic desensitization and social skills training) can be helpful.

Simple Phobias

The classical simple phobia is the fear of small animals, such as snakes or mice. However, the specific fear can concern many other objects or situations perceived as threatening: heights, elevators, airplanes, or blood. Multiple simple phobias may coexist and cause confusion with agoraphobia.

Behavior therapy involves gradual, repeated and prolonged exposure to the feared object or situation, often accompanied by relaxation techniques, until anxiety habituates away.

This is one area where the point of demarcation from normal or trivial fears is especially relevant; the *DSM-III-R* diagnosis requires either that the fear or avoidance of the feared object significantly impairs the individual's functioning, or that the person experiences marked distress about the fear.

The vast majority of simple phobics never seek treatment for their problem, though the treatment of choice, behavioral therapy, is fairly clear-cut and quite effective. Behavior therapy involves gradual, repeated, and prolonged exposure to the feared object or situation, often accompanied by relaxation techniques, until anxiety habituates away.

Obsessive-Compulsive Disorder (OCD)

Obsessions are repetitive, uncomfortable mental experiences that a person tries to suppress. They may take many forms: blasphemous phrases, violent images, persistent doubts, unreasonable fears.

Compulsions are repetitive, senseless behaviors that a person often tries to suppress but also uses to relieve discomfort associated with obsessions. They may also take varied forms: checking, cleaning, arranging things

in specific orders, seeking reassurance from others, and even covert "mental" behavior such as silent prayers.

Compulsions can resemble superstitions. There is a phenomenon of normal obsessions and compulsions that many readers may relate to – for example, having a jingle go around and around in one's head or feeling obliged to "knock on wood" – but these do not cause the wasted time, impairment or distress seen with OCD.

OCD has engendered interest of its possible relationship to certain other disorders such as trichotillomania ("compulsive" hair-pulling), hypochondriasis, and body dysmorphic disorder ("obsessions" with imagined ugliness).[10]

Posttraumatic Stress Disorder (PTSD)

PTSD is a syndrome that may ensue from undergoing an extraordinarily stressful experience: rape, the rigors of war, torture, childhood sexual abuse, or communal catastrophe. Some accidents are psychologically traumatic enough to have this effect. Sexual traumas seem to carry special risk. Typically, the victim keeps reexperiencing the event in the form of flashbacks or nightmares, while making efforts to avoid reminders, even to the point of amnesia for the event itself. There also may be a general "emotional numbness" along with signs of overarousal such as insomnia, irritability, impaired concentration, and or excessive vigilance.

PTSD may affect 1% of the population; this prevalence will vary with specific groups at risk. It is unlike any of the other anxiety disorders in being critically tied to a causative event, so there has been discussion of placing it in a separate group of "stress-related disorders."

Generalized Anxiety Disorder (GAD)

GAD is a syndrome of chronic excessive worry and anxiety, which involves many of the same physical symptoms as panic disorder but on a less intense and more persistent basis. *DSM-III-R* requires that anxiety and excessive worrying be present most days for at least six months, with at least 6 of 18 mostly physical symptoms.

Compulsions are repetitive, senseless behaviors that a person often tries to suppress but also uses to relieve discomfort associated with obsessions.

A fairly new diagnosis, GAD is understudied and sometimes thought epiphenomenal to other disorders with which it commonly coexists, such as panic disorder and major depression. It is rare to find GAD existing in isolation as the sole psychiatric diagnosis of an individual patient. Nevertheless, it may be quite common, with prevalence rates upwards of 2% and is a major indication for benzodiazepines.

Returning to a Broad Perspective

In this article and issue of *Rhode Island Medicine*, the focus is on panic disorder, which has received the most study of late. However, OCD has also recently come into its own and PTSD is a subject of awakening interest. Social phobia and GAD await needed attention.

Generalizations about "the anxiety disorders" may be meaningless since some may require quite separate consideration from the others. One thing they share in common is that all have been, until quite recently, relatively neglected, even "trivialized." This neglect seems unwarranted and trivialization unjust; we can hope that professional and public awareness of their prevalence, impact and potential for effective treatment is increasing.

References

1. American Psychiatric Association, *Diagnostic and Statistical Manual of Mental Disorders* (Third ed, revised), 1987.
2. American Psychiatric Association, *DSM-IV Options Book*, work in progress, 1991.
3. Robins LN, Helzner JE, Weissman MM, *et al.* Lifetime prevalence of specific psychiatric disorders in three sites. *Arch Gen Psychiatry* 41:949-958, 1984.
4. Weissman MM, Merikangas KR. The epidemiology of anxiety and panic disorders: An update. *J Clin Psychiatry* 47 (Suppl):11-17, 1986.
5. Kushner MG, Sher KJ, Beitman BD. The relation between alcohol problems and the anxiety disorders. *Am J Psychiatry* 149:685-695, 1990.
6. Allgulander C, Lavori PW. Excess mortality among 3302 patients with "pure' anxiety neurosis. *Arch Gen Psychiatry* 48:599-602, 1991.
7. Weissman MM, Markowitz JS, Ouellette R, Greenwalk S, Kahn JP. Panic disorder and cardiovascular/cerebrovascular problems: Results from a community survey. *AmJ Psychiatry* 1457:1504-1508, 1990.
8. Wheeler EO, White PD, Reed EW, Cohen ME. Neurocirculatory asthenia (anxiety neurosis, effort syndrome, neurasthenia). *JAMA* 878-889, 1950.
9. Liebowitz MR, Gorman JM, Fyer AJ, *et al.* Social phobia: Review of a neglected anxiety disorder. *Arch Gen Psychiatry* 42:729-736, 1985.
10. Tynes LL, White K, Steketee GS. Towards a new nosology of obsessive compulsive disorder. *Compr Psychiatry* 31:465-480, 1990.

Address correspondence to:
Kerrin White, MD
Providence VA Medical Center
830 Chalkstone Avenue
Providence, RI 02906

The ACCUPRIL Single-Agent Commitment™

Parke-Davis is confident that for many of your hypertensive patients ACCUPRIL will achieve the decrease in blood pressure you expect.

If, in your medical judgment, your patient requires a diuretic in addition to ACCUPRIL at any time during ACCUPRIL therapy, Parke-Davis will refund your patient's cost of the diuretic.*†

New! ONCE-A-DAY ‡

ACCUPRIL®™

quinapril HCl tablets 10, 20, 40 mg

* See DOSAGE AND ADMINISTRATION section of prescribing information.

† If, after an adequate trial of ACCUPRIL alone, based on your medical judgment as the prescribing physician, you determine that your patient requires the addition of a diuretic, Parke-Davis will refund to the patient his/her cost for the diuretic prescription less any amount reimbursed or paid for by an HMO, insurance company, or any other plan or program.

For more details, ask your Parke-Davis Representative or call 1-800-955-3077.

‡ In some patients, the antihypertensive effect may diminish toward the end of the once-daily dosing interval. In such patients, an increase in dosage or twice-daily administration may be warranted.

ACCUPRIL is available in 10, 20, and 40 mg tablets. Usual initial starting dosage is 10 mg once daily.

ACCUPRIL is contraindicated in patients who are hypersensitive to this product and in patients with a history of angioedema related to previous treatment with an ACE inhibitor.

Please see brief summary of prescribing information on following page.

© 1991 Warner-Lambert Company

PARKE-DAVIS

Accupril® (Quinapril Hydrochloride Tablets)

Before prescribing, please see full prescribing information. A brief summary follows.

INDICATIONS AND USAGE

ACCUPRIL is indicated for the treatment of hypertension. It may be used alone or in combination with thiazide diuretics.

In using ACCUPRIL, consideration should be given to the fact that another angiotensin-converting enzyme (ACE) inhibitor, captopril, has caused agranulocytosis, particularly in patients with renal impairment or collagen vascular disease. Available data are insufficient to show that ACCUPRIL does not have a similar risk (see WARNINGS).

CONTRAINDICATIONS

ACCUPRIL is contraindicated in patients who are hypersensitive to this product and in patients with a history of angioedema related to previous treatment with an ACE inhibitor.

WARNINGS

Angioedema: Angioedema of the face, extremities, lips, tongue, glottis, and larynx has been reported in patients treated with ACE inhibitors and has been seen in 0.1% of patients receiving ACCUPRIL. Angioedema associated with laryngeal edema can be fatal. If laryngeal stridor or angioedema of the face, tongue, or glottis occurs, treatment with ACCUPRIL should be discontinued immediately, the patient treated in accordance with accepted medical care, and carefully observed until the swelling disappears. In instances where swelling is confined to the face and lips, the condition generally resolves without treatment, antihistamines may be useful in relieving symptoms.

Where there is involvement of the tongue, glottis, or larynx likely to cause airway obstruction, emergency therapy including, but not limited to, subcutaneous epinephrine solution 1:1000 (0.3 to 0.5 mL) should be promptly administered (see ADVERSE REACTIONS).

Hypotension: Symptomatic hypotension was rarely seen in uncomplicated hypertensive patients treated with ACCUPRIL but, as with other ACE inhibitors, it is a possible consequence of therapy in salt/volume depleted patients, such as those previously treated with diuretics or dietary salt restriction or who are on dialysis (see PRECAUTIONS, DRUG INTERACTIONS, and ADVERSE REACTIONS). In controlled studies, syncope was observed in 0.4% of patients (N = 3203), this incidence was similar to that observed for captopril (1%) and enalapril (0.8%).

In patients with concomitant congestive heart failure, with or without associated renal insufficiency, ACE inhibitor therapy may cause excessive hypotension, which may be associated with oliguria or azotemia and, rarely, with acute renal failure and death. In such patients, ACCUPRIL therapy should be started at the recommended dose under close medical supervision. These patients should be followed closely for the first 2 weeks of treatment and whenever the dosage of antihypertensive medication is increased (see DOSAGE AND ADMINISTRATION).

If symptomatic hypotension occurs, the patient should be placed in the supine position and, if necessary, normal saline may be administered intravenously. A transient hypotensive response is not a contraindication to further doses; however, lower doses of ACCUPRIL or reduced concomitant diuretic therapy should be considered.

Neutropenia/Agranulocytosis: Another ACE inhibitor, captopril, has been shown to cause agranulocytosis and bone marrow depression rarely in patients with uncomplicated hypertension, but more frequently in patients with renal impairment, especially if they also have a collagen vascular disease such as systemic lupus erythematosus or scleroderma. Agranulocytosis did occur during ACCUPRIL treatment in one patient with a history of neutropenia during previous captopril therapy. Available data from clinical trials of ACCUPRIL are insufficient to show that, in patients without prior reactions to other ACE inhibitors, ACCUPRIL does not cause agranulocytosis at similar rates. As with other ACE inhibitors, periodic monitoring of white blood cell counts in patients with collagen vascular disease and/or renal disease should be considered.

Fetal/Neonatal morbidity and mortality: ACE inhibitors, including ACCUPRIL, can cause fetal and neonatal morbidity and mortality when administered to pregnant women.

When ACE inhibitors have been used during the second and third trimesters of pregnancy, there have been reports of hypotension, renal failure, skull hypoplasia, and death. Oligohydramnios has also been reported, presumably resulting from decreased fetal renal function; oligohydramnios has been associated with fetal limb contractures, craniofacial deformities, hypoplastic lung development, and intrauterine growth retardation.

Prematurity and patent ductus arteriosus have been reported, although it is not clear whether these occurrences were due to the ACE-inhibitor exposure or to the mother's underlying disease. It is not known whether exposure limited to the first trimester can adversely affect fetal outcome.

A patient who becomes pregnant while taking ACE inhibitors, or who takes ACE inhibitors when already pregnant, should be apprised of the potential hazard to her fetus. If she continues to receive ACE inhibitors during the second or third trimester of pregnancy, frequent ultrasound examinations should be performed to look for oligohydramnios. When oligohydramnios is found, ACE inhibitors should generally be discontinued.

Infants with histories of in utero exposure to ACE inhibitors should be closely observed for hypotension, oliguria, and hyperkalemia. If oliguria occurs, attention should be directed toward support of blood pressure and renal perfusion. Hemodialysis and peritoneal dialysis have little effect on the elimination of quinapril and quinaprilat.

No fetotoxic or teratogenic effects were observed in rats at quinapril doses as high as 300 mg/kg/day (180 and 30 times the maximum daily human dose when based on mg/kg and mg/m², respectively), despite maternal toxicity at 150 mg/kg/day. Tested later in gestation and during lactation, reduced offspring body weight was seen at ≥25 mg/kg/day, and changes in renal histology (juxtaglomerular cell hypertrophy, tubular/pelvic dilation, glomerulosclerosis) were observed both in dams and offspring treated with 150 mg/kg/day. Quinapril was not teratogenic in the rabbit, however, as noted with other ACE inhibitors, maternal toxicity and embryotoxicity were seen in some rabbits at quinapril doses as low as 0.5 mg/kg/day (one time the recommended human dose) and 1.0 mg/kg/day, respectively.

PRECAUTIONS

General

Impaired renal function: As a consequence of inhibiting the renin-angiotensin-aldosterone system, changes in renal function may be anticipated in susceptible individuals. In patients with severe heart failure whose renal function may depend on the activity of the renin-angiotensin-aldosterone system, treatment with ACE inhibitors, including ACCUPRIL, may be associated with oliguria and/or progressive azotemia and rarely acute renal failure and/or death.

In clinical studies in hypertensive patients with unilateral or bilateral renal artery stenosis, increases in blood urea nitrogen and serum creatinine have been observed in some patients following ACE inhibitor therapy. These increases were almost always reversible upon discontinuation of the ACE inhibitor and/or diuretic therapy. In such patients, renal function should be monitored during the first few weeks of therapy.

Some hypertensive patients with no apparent preexisting renal vascular disease have developed increases in blood urea and serum creatinine, usually minor and transient, especially when ACCUPRIL has been given concomitantly with a diuretic. This is more likely to occur in patients with preexisting renal impairment. Dosage reduction and/or discontinuation of any diuretic and/or ACCUPRIL may be required.

Evaluation of hypertensive patients should always include assessment of renal function (see DOSAGE AND ADMINISTRATION).

Hyperkalemia and potassium-sparing diuretics: In clinical trials, hyperkalemia (serum potassium ≥5.8 mmol/L) occurred in approximately 2% of patients receiving ACCUPRIL. In most cases, elevated serum potassium levels were isolated values which resolved despite continued therapy. Less than 0.1% of patients discontinued therapy due to hyperkalemia. Risk factors for the development of hyperkalemia include renal insufficiency, diabetes mellitus, and the concomitant use of potassium-sparing diuretics, potassium supplements, and/or potassium-containing salt substitutes, which should be used cautiously, if at all, with ACCUPRIL (see PRECAUTIONS, Drug Interactions).

Surgery/anesthesia: In patients undergoing major surgery or during anesthesia with agents that produce hypotension, ACCUPRIL will block angiotensin II formation secondary to compensatory renin release. If hypotension occurs and is considered to be due to this mechanism, it can be corrected by volume expansion.

Information for Patients

Angioedema: Angioedema, including laryngeal edema, can occur with treatment with ACE inhibitors, especially following the first dose. Patients should be so advised and told to report immediately any signs or symptoms suggesting angioedema (swelling of face, extremities, eyes, lips, tongue, difficulty in swallowing or breathing) and to stop taking the drug until they have consulted with their physician (see WARNINGS).

Symptomatic hypotension: Patients should be cautioned that lightheadedness can occur, especially during the first few days of ACCUPRIL therapy, and that it should be reported to a physician. If actual syncope occurs, patients should be told to not take the drug until they have consulted with their physician (see WARNINGS).

All patients should be cautioned that inadequate fluid intake or excessive perspiration, diarrhea, or vomiting can lead to an excessive fall in blood pressure because of reduction in fluid volume, with the same consequences of lightheadedness and possible syncope.

Patients planning to undergo any surgery and/or anesthesia should be told to inform their physician that they are taking an ACE inhibitor.

Hyperkalemia: Patients should be told not to use potassium supplements or salt substitutes containing potassium without consulting their physician (see PRECAUTIONS).

Accupril® (Quinapril Hydrochloride Tablets)

Neutropenia: Patients should be told to report promptly any indication of infection (eg, sore throat, fever) which could be a sign of neutropenia.

NOTE: As with many other drugs, certain advice to patients being treated with ACCUPRIL is warranted. This information is intended to aid in the safe and effective use of this medication. It is not a disclosure of all possible adverse or intended effects.

Drug Interactions

Concomitant diuretic therapy: As with other ACE inhibitors, patients on diuretics, especially those on recently instituted diuretic therapy, may occasionally experience an excessive reduction of blood pressure after initiation of therapy with ACCUPRIL. The possibility of hypotensive effects with ACCUPRIL may be minimized by either discontinuing the diuretic or cautiously increasing salt intake prior to initiation of treatment with ACCUPRIL. If it is not possible to discontinue the diuretic, the starting dose of quinapril should be reduced (see DOSAGE AND ADMINISTRATION).

Agents increasing serum potassium: Quinapril can attenuate potassium loss caused by thiazide diuretics and increase serum potassium when used alone. If concomitant therapy of ACCUPRIL with potassium-sparing diuretics (eg, spironolactone, triamterene, or amiloride), potassium supplements, or potassium-containing salt substitutes is indicated, they should be used with caution along with appropriate monitoring of serum potassium (see PRECAUTIONS).

Tetracycline and other drugs that interact with magnesium: Simultaneous administration of tetracycline with ACCUPRIL reduced the absorption of tetracycline by approximately 28% to 37%, possibly due to the high magnesium content in ACCUPRIL tablets. This interaction should be considered if coprescribing ACCUPRIL and tetracycline or other drugs that interact with magnesium.

Lithium: Increased serum lithium levels and symptoms of lithium toxicity have been reported in patients receiving concomitant lithium and ACE inhibitor therapy. These drugs should be co-administered with caution, and frequent monitoring of serum lithium levels is recommended. If a diuretic is also used, it may increase the risk of lithium toxicity.

Other agents: Drug interaction studies of ACCUPRIL with other agents showed:

- Multiple dose therapy with propranolol or cimetidine has no effect on the pharmacokinetics of single doses of ACCUPRIL.
- The anticoagulant effect of a single dose of warfarin (measured by prothrombin time) was not significantly changed by quinapril coadministration twice-daily.
- ACCUPRIL treatment did not affect the pharmacokinetics of digoxin.
- No pharmacokinetic interaction was observed when single doses of ACCUPRIL and hydrochlorothiazide were administered concomitantly.

Carcinogenesis, Mutagenesis, Impairment of Fertility

Quinapril hydrochloride was not carcinogenic in mice or rats when given in doses up to 75 or 100 mg/kg/day (50 to 60 times the maximum human daily dose, respectively, on a mg/kg basis and 3.8 to 10 times the maximum human daily dose when based on a mg/m² basis) for 104 weeks. Female rats given the highest dose level had an increased incidence of mesenteric lymph node hemangiomas and skin/subcutaneous lipomas. Neither quinapril nor quinaprilat were mutagenic in the Ames bacterial assay with or without metabolic activation. Quinapril was also negative in the following genetic toxicology studies: *in vitro* mammalian cell point mutation, sister chromatid exchange in cultured mammalian cells, micronucleus test with mice, *in vitro chromosome* aberration with V79 cultured lung cells, and in an *in vivo* cytogenetic study with rat bone marrow. There were no adverse effects on fertility or reproduction in rats at doses up to 100 mg/kg/day (60 and 10 times the maximum daily human dose when based on mg/kg and mg/m², respectively).

Pregnancy

Pregnancy Category D. See WARNINGS, Fetal/Neonatal morbidity and mortality.

Nursing Mothers

It is not known if quinapril or its metabolites are secreted in human milk. Quinapril is secreted to a limited extent, however, in milk of lactating rats (5% or less of the plasma drug concentration was found in rat milk). Because many drugs are secreted in human milk, caution should be exercised when ACCUPRIL is given to a nursing mother.

Geriatric Use

Elderly patients exhibited increased area under the plasma concentration time curve (AUC) and peak levels for quinaprilat compared to values observed in younger patients, this appeared to relate to decreased renal function rather than to age itself. In controlled and uncontrolled studies of ACCUPRIL where 918 (21%) patients were 65 years and older, no overall differences in effectiveness or safety were observed between older and younger patients. However, greater sensitivity of some older individual patients cannot be ruled out.

Pediatric Use

The safety and effectiveness of ACCUPRIL in children have not been established.

ADVERSE REACTIONS

ACCUPRIL has been evaluated for safety in 4960 subjects and patients. Of these, 3203 patients, including 655 elderly patients, participated in controlled clinical trials. ACCUPRIL has been evaluated for long-term safety in over 1400 patients treated for 1 year or more.

Adverse experiences were usually mild and transient.

Discontinuation of therapy because of adverse events was required in 4.7% of patients treated with ACCUPRIL in placebo-controlled hypertension trials.

Adverse experiences probably or possibly related to therapy or of unknown relationship to therapy occurring in 1% or more of the 1563 patients in placebo-controlled hypertension trials who were treated with ACCUPRIL are shown below.

Adverse Events in Placebo-Controlled Trials

	ACCUPRIL (N = 1563) Incidence (Discontinuance)	Placebo (N = 579) Incidence (Discontinuance)
Headache	5.6 (0.7)	10.9 (0.7)
Dizziness	3.9 (0.8)	2.6 (0.2)
Fatigue	2.6 (0.3)	1.0
Coughing	2.0 (0.5)	0.0
Nausea/Vomiting	1.4 (0.3)	1.9 (0.2)
Abdominal Pain	1.0 (0.2)	0.7

Clinical adverse experiences probably or possibly related, or of uncertain relationship to therapy, occurring in 0.5% to 1.0% (except as noted) of the patients treated with ACCUPRIL (with or without concomitant diuretic) in controlled or uncontrolled trials (N = 4397) and less frequent, clinically significant events seen in clinical trials or post-marketing experience (the rarer events are in italics) include (listed by body system):

General: back pain, malaise

Cardiovascular: palpitation, vasodilation, tachycardia, *heart failure, hyperkalemia, myocardial infarction, cerebrovascular accident, hypertensive crisis, angina pectoris, orthostatic hypotension, cardiac rhythm disturbances*

Gastrointestinal: dry mouth or throat, constipation, *gastrointestinal hemorrhage, pancreatitis, abnormal liver function tests*

Nervous/Psychiatric: somnolence, vertigo, syncope, *nervousness, depression*

Integumentary: increased sweating, pruritus, *exfoliative dermatitis, photosensitivity reaction*

Urogenital: *acute renal failure*

Other: amblyopia, pharyngitis, sinusitis, bronchitis, *agranulocytosis, thrombocytopenia*

Angioedema: angioedema has been reported in patients receiving ACCUPRIL (0.1%). Angioedema associated with laryngeal edema may be fatal. If angioedema of the face, extremities, lips, tongue, glottis, and/or larynx occurs, treatment with ACCUPRIL should be discontinued and appropriate therapy instituted immediately. (See WARNINGS.)

Clinical Laboratory Test Findings

Hematology: (See WARNINGS)

Hyperkalemia: (See PRECAUTIONS)

Creatinine and blood urea nitrogen: Increases (>1.25 times the upper limit of normal) in serum creatinine and blood urea nitrogen were observed in 2% and 2%, respectively, of patients treated with ACCUPRIL alone. Increases are more likely to occur in patients receiving concomitant diuretic therapy than in those on ACCUPRIL alone. These increases often remit on continued therapy.

* In some patients, the antihypertensive effect may diminish toward the end of the once-daily dosing interval. In such patients, an increase in dosage or twice-daily administration may be warranted.

New!
ONCE-A-DAY
ACCUPRIL™
quinapril HCl tablets

PARKE-DAVIS
Division of Warner-Lambert Company
Morris Plains, New Jersey 07950

PD-103-JA-7164-A2(022)

Neurobiological Aspects of Panic Disorder

Gary B. Kaplan, MD

An understanding of the pathophysiology of panic disorder ultimately will result in advances in the treatment of panic disorder.

Investigators are seeking to delineate the neuroanatomical pathways and the neurotransmitter and neuropharmacological mechanisms that underlie anxiety and panic disorders. An understanding of the pathophysiology of panic disorder ultimately will result in advances in its treatment, bringing greater relief to patients who suffer from this widely prevalent and chronic condition with its associated medical, interpersonal and financial disabilities.

There are a variety of approaches for studying the neurobiological mechanisms of panic disorder. In preclinical studies, investigators can measure relevant aspects of the pathophysiology of anxiety directly. The neurotransmitter systems that are implicated most commonly in the etiology of panic disorder are norepinephrine, serotonin and gamma-aminobutyric acid (GABA). Animal studies modeling anxious behaviors can measure associated alterations in neurotransmitters, receptor binding, neuronal intracellular pathways, pharmacological responsivity, neuronal electrophysiology and even gene induction.

Clinical studies are also important in the study of the neurobiology of panic disorder. Neuroanatomical differences in persons with panic disorder compared to healthy volunteers can be explored using a variety of brain imaging techniques. Neurotransmitter difference in panic patients vs controls can be studied by measuring neurotransmitters or their metabolites in cerebrospinal fluid, plasma or urine. Peripheral cell receptors (ie, measured on platelets and lymphocytes) can be examined in panic patients; as it is hypothesized peripheral receptor abnormalities reflect alterations of the same receptors in the central nervous system. Pharmacological challenge studies in panic patients can delineate abnormal behavioral, biochemical and neuroendocrine responses to drugs that act as neurotransmitter agonists and antagonists. Alterations in pharmacological response in panic patients also may reflect central receptor abnormalities in these patients.

Gary B. Kaplan, MD, is Assistant Professor of Psychiatry and Human Behavior, Brown University, Providence, Rhode Island.

Neuroanatomy of Anxiety

The limbic system is a neuroanatomical region that has been hypothesized as having an important role in the experiencing and the expression of anxiety. This highly interconnected circuit includes the hypothalamus, amygdala, anterior thalamus, cingulate gyrus, hippocampus and various other inputs and projections. The inputs send somatosensory, visual and auditory information to primary sensory regions and sensory association regions that project to the amygdala and hippocampus. These latter two regions, in association with higher cortical regions, can evaluate highly processed sensory information. Expression of anxiety occurs via projections to the midbrain, brain stem, hypothalamus and thoracic spinal cord. These outputs mediate cardiovascu-

ABBREVIATIONS USED:
beta-CCE: beta-carboline-3-carboxylate ethyl ester
CCK: cholecystokinin
GABA: gamma-aminobutyric acid
5HT: 5-hydroxytyptamine (serotonin)
MAOI: monoamine oxidase inhibitor
MHPG: 3-methoxy-4-hydroxyphenylglycol
mCPP: m-chlorophenylpiperazine
PET: positron emission tomography

lar, neuroendocrine and autonomic responses of anxiety such as tachycardia, diaphoresis, hyperventilation and cortisol secretion.[1]

Studies have examined the hypotheses that specific brain regions in the limbic system mediate anxiety and that focal abnormalities are found in panic disorder patients. Positron emission tomography (PET) scanning is an imaging technique used to visualize cerebral blood flow and brain metabolism in humans. PET scans, comparing a subpopulation of panic disorder patients in a resting state to normal volunteers, found that the panic patients had an abnormal asymmetry in parahippocampal blood flow, blood volume and oxygen metabolism. This suggests that the PET asymmetry reflects an increase in right parahippocampal activity in these patients and that it has a role in their vulnerability to panic attacks. Another PET study in panic patients demonstrated bilateral increases in blood flow to temporo-limbic regions during their panic attacks. The temporal cortex receives inputs from sensory association areas and limbic structures, suggesting its role in interpreting internally or externally perceived threats and mediating behavioral and physiological responses.[2]

The locus coeruleus is a nucleus located in the pons that is thought to have an important role in anxiety. It contains nearly half the norepinephrine-containing neurons in the brain and produces over 70% of the total norepinephrine in primate brain. It has afferent connections from many regions and provides the principal noradrenergic innervation to the cerebral cortex, limbic system, brain stem and spinal cord. The locus coeruleus appears to have an alarm function and alerts the organism to threats of danger and mediates the expression of fear- and stress-related responses. Electrical or pharmacological stimulation (eg, administration of the alpha$_2$-adrenergic antagonist drug yohimbine) of this nucleus in primates induces fear-related behaviors such as scratching, hand-wringing, teeth-grinding, yawning, hair-pulling and attempts at escape. Electrolytic lesioning or pharmacological blockade (eg, administration of the beta-adrenergic antagonist drug propranolol) of the locus coeruleus reduces neuronal firing of this region and blocks these behaviors.[3] Table 1 presents a summary of neuroanatomical findings in panic disorder.

Table 1. **Neuroanatomy of Panic Disorder**

Neuroanatomical region	Abnormal findings and role in panic
Parahippocampal gyrus	Abnormal asymmetry in blood flow, volume and metabolism in panic patients at rest. Role in the triggering of panic attacks.
Temporal cortex	Increased blood flow in patients experiencing lactate-induced panic attacks. Role in interpreting internally or externally perceived threats.
Locus coeruleus	Stimulation of nucleus results in fear-related behaviors in primates; lesioning of pharmacological blockade of nucleus results in inhibition of these behaviors. Role as an alarm mechanism, alerting the organism to danger.

Noradrenergic Mechanisms

It is hypothesized that panic disorder patients are vulnerable to panic attacks because of a dysregulation of noradrenergic function. Following emotional stress, normal subjects have increased levels of norepinephrine and epinephrine and their metabolites in plasma and urine. Significant positive correlations have been found between anxiety ratings and norepinephrine and metabolite concentrations in the cerebrospinal fluid of patients with depression. In panic disorder patients, elevated levels of epinephrine but not norepinephrine have been found. Plasma 3-methoxy-4-hydroxyphenylglycol (MHPG), a catecholamine metabolite, has been used as an indirect measure of noradrenergic activity. Several studies have demonstrated abnormalities in plasma MPHG in panic disorder patients.[4]

Several types of adrenergic receptors are found in the mammalian brain that differ in their location and functional properties. The beta-adrenergic receptor subtype may be altered in panic disorder patients. Pharmacological challenge studies using the beta-adrenergic agonist agent, isoproterenol, have been performed in panic disorder patients vs normal controls. Panic attacks were provoked more frequently in the patient group. Conversely, the beta-adrenergic antagonist propranolol blocked many of the somatic symptoms of anxiety and panic in these patients. Additionally, alterations in beta-adrenergic receptor density and affinity have been found in plasma lymphocytes in patients with panic disorder, reflecting central adrenoreceptor abnormalities.[4]

It has been suggested that the alpha$_2$-adrenoreceptor and its intracellular effector systems are altered in panic disorder. Both increases and decreases in responsivity to alpha$_2$ adrenergic agonist clonidine have been demonstrated in panic patients vs healthy volunteers. Panic patients have greater responsivity to clonidine-induced effects on blood pressure, cortisol and plasma MHPG levels than controls. Panic patients also have decreased responsivity to the sedative and growth hormone stimulating effects of clonidine. When a subgroup of panic

disorder patients are administered the alpha$_2$-adrenergic antagonist yohimbine, they more frequently experience panic attacks and have greater increases in blood pressure and plasma MHPG levels than healthy volunteers. Studies examining peripheral cell receptors in panic subjects have shown abnormalities in platelet alpha$_2$-adrenoreceptor binding. These studies suggest that abnormal regulation of noradrenergic neuronal systems contributes to the pathophysiology of panic attacks, but the exact nature and direction of these alterations is unclear.[4]

Serotonergic Mechanisms

Like adrenoreceptors, there are several types of serotonin receptors that differ in their distribution and functional properties. One subtype, the 5HT$_{1A}$ receptor, is found in the amygdala and hippocampus and is thought to have a role in anxiety. Agonists at the 5HT$_{1A}$ receptor, such as buspirone, are effective clinically as anxiolytic agents (but not as anti-panic agents) and may work by altering limbic functioning. Preclinical studies have demonstrated that a variety of serotonin agonist and antagonist drugs and serotonergic reuptake inhibitors have anxiolytic effects in animal models of anxiety. Serotonin decreases locus coeruleus firing in pre-clinical studies. This suggests that interactions between serotonergic and noradrenergic systems are important in the mediation of anxiety.[5]

Only a few clinical investigations have been performed examining serotonin function in panic disorder patients, and several of these demonstrated no abnormalities. There were no differences in serotonin metabolite concentration in cerebrospinal fluid in panic patients vs controls. Alterations in the rate of serotonin uptake in platelets were found in panic patient groups vs healthy volunteers.

The strongest evidence of a role for serotonin in panic disorder has come from pharmacological challenge studies. One such study showed that an agent that enhances presynaptic serotonin release, fenfluramine, produced greater increases in anxiety and neuroendocrine responses in panic patients vs controls. Another showed that a serotonin receptor agonist, m-chlorophenyl-piperazine (mCPP), caused greater increases in anxiety and neuroendocrine response in panic patients. There has been strong evidence for the efficacy of drugs that act as selective serotonin reuptake blockers, such as fluoxetine and fluvoxamine, in the treatment of panic disorder. In sum, these studies suggest a role for serotonin in mediating panic states but do not elucidate the specific nature of the alterations. Most promising has been the development of future anxiolytics that include serotonin reuptake blockers and 5HT agonist and antagonist drugs.[5]

Benzodiazepine/GABA Receptor Mechanisms

Pre-clinical studies have established the existence of a structural and functional model for the benzodiazepine/ GABA receptor complex in the brain. Benzodiazepines have anxiolytic, muscle-relaxant and anticonvulsant effects that are mediated by this receptor. Benzodiazepines bind to their own recognition site on this receptor complex and enhance the binding of the neurotransmitter GABA to its separate binding site, also on the complex. GABA binding to its recognition site results in the opening of an associated chloride channel. The movement of chloride ions into the neuron results in negative potential across the cell membrane. Benzodiazepine-induced enhancement of GABA binding results in increased frequency of chloride channel openings and increased chloride flux into the cells. This hyperpolarization of neuronal cells by benzodiazepine drugs is thought to result in their anxiolytic effects.

The importance of the benzodiazepine/GABA receptor complex, and of benzodiazepine drugs, has been illustrated by a variety of pre-clinical and clinical studies. Beta-CCE is a drug that has high affinity for the benzodiazepine receptor and induces the opposite effects of benzodiazepines, including anxiogenic and proconvulsant effects. For this reason, it is known as a benzodiazepine inverse agonist. When administered to primates, it induces the following anxiety-related behaviors and physiological changes: grimacing, teeth-baring, increased vocalizations and elevations in heart rate, blood pressure, plasma cortisol and catecholamine levels. Administration of diazepam, a benzodiazepine agonist, blocks the effects of this agent. When beta-CCE is administered to healthy adults, it induces symptoms of motor tension, apprehension and elevations in heart rate and blood pressure that are reversed by benzodiazepines. A variety of novel benzodiazepine partial agonists are being examined as anxiolytic agents with potentially fewer side effects than benzodiazepines currently used.[6]

Lactate-induced panic is accompanied by physiological alterations including elevations in heart rate, blood pressure, blood lactate, pyruvate and bicarbonate levels, with decreases in blood calcium and phosphorus.

Attempts to quantify benzodiazepine/GABA receptors in the human brain have been undertaken by administering radioactively labelled benzodiazepines to humans and imaging brain regions using PET scanning. These studies in healthy volunteers show that receptor binding is greatest in the cortex, cerebellum and thalamus. Further studies will be undertaken to measure these receptors in psychiatric populations. Pharmacologic challenge studies have been performed with panic disorder patients using a variety of neuroendocrine, behavioral and physiological measures of benzodiazepine responses. Saccadic eye velocity is a highly quantifiable dose-dependent measure of benzodiazepine receptivity in healthy volunteers. Follow-up studies in panic disorder patients, using this pharmacodynamic

Table 2. **Neurotransmitter Abnormalities in Panic Disorder Patients**

Neurotransmitter	Clinical findings in panic patients
Norepinephrine	• Elevated plasma epinephrine levels and altered plasma MHPG levels • Altered adrenoreceptor binding and second messenger formation in platelets and lymphocytes • Anxiogenic and abnormal neuroendocrine responses to adrenergic agents yohimbine and isoproterenol
Serotonin	• No alterations in 5HT metabolite levels in cerebrospinal fluid • Alterations in 5HT uptake in platelets • Anxiogenic and abnormal neuroendocrine responses to serotonergic agents mCPP and fenfluramine
GABA/benzodiazepine	• Anxiogenic effects of benzodiazepine inverse agonists which are reversed by benzodiazepine agonists • Decreased physiological sensitivity to benzodiazepines

parameter, demonstrate that these patients are significantly less sensitive to diazepam than normal volunteers. This reduced sensitivity may relate to a reduced benzodiazepine/GABA receptor number or binding affinity or to alteration in receptor function. A receptor alteration such as this could represent a potential triggering mechanism for panic attacks.[7] Table 2 presents a summary of neurotransmitter and receptor alterations found in panic disorder subjects.

Panic-Inducing Agents: Lactate, Caffeine, Cholecystokinin

Sodium lactate was one of the first pharmacological challenge agents used to study the etiology of panic attacks. In a wide range of studies, about 70% of panic disorder patients developed panic attacks after lactate infusions, while few healthy subjects developed panic symptoms. This response rate was specific to panic disorder patients and was not as high for patients with other anxiety disorders. Lactate-induced panic is accompanied by physiological alterations including elevations in heart rate, blood pressure, blood lactate, pyruvate and bicarbonate levels, with decreases in blood calcium and phosphorus. Hypotheses about the mechanism of lactate-induced panic focus on the locus coeruleus and on chemoreceptor sensitivity alterations. Other proposed mechanisms of lactate-induced panic involve its regulation of intracellular pH, various ion pumps, cellular phosphorylation states and the calcium/calmodulin system.[8]

Much research literature describes the anxiogenic and panic-inducing effects of caffeine. Caffeine induces anxiety in normal subjects at doses of 10 mg/kg (one cup of coffee is approximately 100 mg to 150 mg) and consistently provokes panic attacks in patients with panic disorder. The clinical syndrome of caffeinism or caffeine toxicity is indistinguishable from some types of anxiety states. A positive correlation between daily caffeine consumption and anxiety scores is demonstrated in patients with anxiety disorders. In a variety of self-administration paradigms in normal volunteers, caffeine reliably induces increases in ratings of stimulation, anxiety and jittering. Caffeine may mediate anxiety by binding to brain adenosine receptors inhibiting the effects of endogenous adenosine at this site. Adenosine is a neurotransmitter with anxiolytic, sedating and motor depressant effects, and adenosine agonists are being examined as novel anxiolytic agents. Cholecystokinin (CCK) is a neurotransmitter in the central nervous system with anxiogenic effects in healthy subjects. CCK administration in panic disorder patients provokes panic symptoms at a much higher rate than found for healthy controls. Various CCK antagonists have been demonstrated as effective anxiolytic agents in pre-clinical studies and may prove useful to clinics in the future.

These pre-clinical and clinical neurochemical and pharmacological studies suggest that multiple neurotransmitter systems are important in mediation of panic states. There is evidence that these different agonist or antagonist drugs produce similar anxiogenic or panic-provoking effects in panic disorder patients via different neurotransmitter and receptor mechanisms.

Psychopharmacology of Panic Disorder

The most effective treatments for panic disorder are tricyclic antidepressants, monoamine oxidase inhibitors, serotonin reuptake inhibitors and benzodiazepines. (Alexander and Gordon discuss the clinical use of these agents in this issue of *Rhode Island Medicine*.) Understanding the mechanisms of action of these drugs may increase our understanding of the neurobiological basis of panic disorder.

Tricyclic antidepressants and monoamine oxidase inhibitors have a variety of effects on noradrenergic systems. Pre-clinical studies show that chronic treatment with antidepressant drugs result in decreases in locus coeruleus firing, norepinephrine turnover and behavioral responses to beta-adrenergic agonists. Chronic treatment also results in decreased beta-adrenoreceptor number and norepinephrine-induced second messenger formation. The decreases in locus coeruleus activity and adrenoreceptor

number and function may account for the anxiolytic effects of these agents. The biochemical alteration produced by antidepressants may block the surge of noradrenergic activity that is associated with anxiety.

Pre-clinical studies have shown that chronic treatment with tricyclic antidepressants, monoamine oxidase inhibitors and serotonin reuptake blockers (eg, fluoxetine) enhances serotonergic function, as measured by electrophysiological and behavioral methods. Chronic antidepressant treatment results in increases in neuronal electrical activity in serotonergic tracts in the brain. Treatment induces down-regulation of 5HT inhibitory autoreceptors (net result is increase in serotonergic function) and an enhancement of coupling of 5HT postsynaptic receptors to their signal transduction and effector mechanisms. Table 3 presents a summary of panic-provoking and anti-panic drugs and their proposed mechanisms of action.

Table 3. **Pharmacological Agents Which Provoke and Relieve Panic**

Panic-provoking agents	**Mechanism of action**
Isoproterenol	• Beta-adrenoreceptor agonist
Yohimbine	• Alpha$_2$-adrenoreceptor antagonist
Fenfluramine	• Enhances presynaptic 5HT release
mCPP	• 5HT$_1$ receptor agonist
beta-CCE	• GABA/benzodiazepine receptor inverse agonist
Sodium lactate	• Noradrenergic effects, regulation of intracellular ions
Caffeine	• Adenosine receptor antagonist
Cholecystokinin	• CCK receptor agonist
Anti-panic agents	
Propranolol	• Beta-adrenoreceptor antagonist
Clonidine	• Alpha$_2$-adrenoreceptor agonist
Fluoxetine	• 5HT reuptake blocker
Buspirone	• 5HT$_{1A}$ receptor agonist
Benzodiazepine	• GABA/benzodiazepine receptor agonist
Tricyclic antidepressants/MAO inhibitors	• Chronic effects-decreased number and function of adrenoreceptors and second messengers and enhanced 5HT function

Summary

The limbic system, temporal cortex and the locus coeruleus are important brain regions in the neuroanatomy of panic states. There is evidence for beta- and alpha$_2$-adrenoreceptor abnormalities and pre- and post-synaptic serotonergic alterations in panic disorder subjects. The anti-panic effects of chronic antidepressant drug treatment may relate to their down-regulation of various components of noradrenergic function and overall enhancement of serotonergic function. The efficacy of benzodiazepine agents in panic disorder and the altered sensitivity of panic patients to benzodiazepine agonists and inverse agonists suggest that alterations in benzodiazepine/GABA receptors may have a role in this disorder. A variety of other pharmacological agents also provoke panic, demonstrating that the biological origins of this disorder are quite diverse and complicated. Most importantly, a variety of new agents that selectively affect different components of these neurotransmitter/receptor systems are being developed. These novel agents offer future promise of greater efficacy with less adverse effects for individuals with panic disorder.

References

1. Reiman EM. The quest to establish the neural substrates of anxiety. *Psychiatric Clinics of North America* 11:295-307, 1988.
2. Reiman EM, Raickle ME, Robins E, Mintun MA, Fusselman MJ, Fox PT, Price JL, Hackman KA. Neuroanatomical correlates of a lactate-induced anxiety attack. *Arch Gen Psychiatry* 46:493-500, 1989.
3. Redmond DE, Huang YH. New evidence for a locus coeruleus-norepinephrine connection with anxiety. *Life Sciences* 25:2149-2162, 1979.
4. Charney DS, Woods SW, Nagy LM, Southwick SM, Krystal JH, Heninger GR Noradrenergic function in panic disorder. *J Clin Psychiatry* (12 Suppl A) 51:5-11, 1990.
5. Charney DS, Krystal JJ, Southwick SM, Nagy LM, Woods SW, Heninger GR. Serotonin function in panic and generalized anxiety disorders. *Psychiatric Annals* 20:593-602, 1990.
6. Brier A, Paul SM. The GABA/benzodiazepine receptor: Implications for the molecular basis of anxiety. *J Psychiatry Research* 24 (Suppl 2):91-104, 1990.
7. Roy-Byrne PP, Cowley DS, Greenblatt DJ, Shader RI, Horrer D. Reduced benzodiazepine sensitivity in panic disorder. *Arch Gen Psychiatry* 47:534-538, 1990.
8. Shear MK. Pathophysiology of panic: A review of pharmacologic provocative tests and naturalistic monitoring data. *J Clin Psychiatry* 46 (Suppl 6):18-26, 1986.

THE NEWLY APPROVED MEDICAL ASSOCIATION TRUSTS

(Summit Bancorporation, Trustee)
(CoreStates Bank, Trustee)

* V.E.B.A. PLAN

FEATURES

UNLIMITED TAX DEDUCTIBLE CONTRIBUTIONS

REGARDLESS OF YOUR PENSION SITUATION

AND IS NOW

IRS APPROVED FOR USE BY DOCTORS IN OTHER STATES

EVEN IF . . .

- YOUR PENSION PLAN IS OVER FUNDED
- YOUR PENSION PLAN IS MAXIMUM FUNDED
- YOU HAVE NO PENSION PLAN

PLEASE SEND ME A copy of the I.R.S. "Favorable Letter of Determination" and other relevant information on your *V.E.B.A. Plan

NAME _____

ADDRESS _____

DATE OF BIRTH _____ TELEPHONE # (____) _____

Mail to: THE KIRWAN COMPANIES
402 MIDDLETOWN BLVD., SUITE 202
LANGHORNE, PA 19047

(800) 969-7666 ..... (215) 750-7616 ..... FAX (215) 750-7791

*VOLUNTARY EMPLOYEE BENEFITS ASSOCIATION

Treatment of Panic Disorder

Paul E. Alexander, MD

Panic disorder is a complex condition that often requires a multifaceted treatment approach, including both medication and cognitive-behavioral treatment.

Despite the biological basis of panic attacks and their responsiveness to medication, most panic patients require more than just medication. Panic disorder is a complex condition that often requires a multifaceted treatment approach. Sheehan and Soto defined four aspects of comprehensive treatment.[1] The core medical symptoms of panic are treated with medication with a goal of complete elimination of both full panic attacks and the limited symptom attacks. The phobic avoidance behavior is treated with cognitive-behavioral treatment. The change in self-esteem, social isolation, family stresses, and vocational reintegration are the subjects of a psychodynamic and supportive psychotherapy. The long-term course, the need for continued follow-up, and relapse prevention are the primary topics of education in the final part of the treatment plan.

Paul E. Alexander, MD, is Clinical Assistant Professor of Psychiatry and Human Behavior, Brown University, Providence, Rhode Island, and Medical Director, Psychiatric Specialists, Inc., Pawtucket, Rhode Island. *This paper is a revision of an earlier published article: "Management of Panic Disorders,"* Journal of Psychoactive Drugs *23:329-333, 1991.*

Patients with panic disorder without agoraphobia, who have had panic attacks for only a few weeks may not require psychosocial treatment. Their treatment can be medication alone, often by the primary care physician. Most patients who seek help for this condition, however, have the associated problems of phobic avoidance behavior and much psychological, familial, and social upheaval requiring comprehensive psychiatric intervention. Early pharmacological treatment to block panic attacks usually leads to the prevention of these associated difficulties.

The focus of the present article is on pharmacological management. Pharmacotherapy is the primary treatment modality for blocking panic attacks. Antidepressants,[2] monoamine oxidase inhibitors (MAOIs),[3] and benzodiazepines[4] have all proven to be effective in double-blind, placebo-controlled studies. The physician's decision on which type of medication to start with depends on a number of factors, because risks and benefits are associated with each drug group.

Initiating Treatment

The management of panic starts with educating the patient, who should be informed that the problem is medical in origin and is a well-defined entity. This information usually relieves the patient of feelings of shame and failure and of a sense of having a strange or unique problem. A physician is best suited to be the primary clinician in the treatment, even if other therapists are involved. It is usually worthwhile to educate the patient about the medical evidence, including the provocative tests that cause panic only in patients who suffer from panic; these tests include sodium lactate,[5] carbon dioxide[6], yohimbine,[7] and caffeine.[8] The finding that positron-emission tomography reveals asymmetrical blood flow in the parahippocampal gyrus only in panic patients lends anatomical evidence.[9] It is also useful to explain that about two-thirds of panic patients have relatives with the same disorder.[10]

Patients should be informed that caffeine and other stimulants can aggravate anxiety and cause panic attacks. Therefore, panic patients should be told to avoid the consumption of caffeine in drinks, such as coffee, tea

ABBREVIATIONS USED:

MAOIs: monoamine oxidase inhibitors

and soda, and large amounts of chocolate. Alcohol tends to reduce anxiety transiently, but frequently one or two drinks can cause a rebounding of increased anxiety hours later or even the next day, so patients should be told to abstain completely. Marijuana and cocaine can cause panic attacks in susceptible individuals. Pseudoephedrine, a medication used alone or in combination cold remedies to relieve congestion, causes many symptoms of anxiety, so patients should be discouraged from its use.

Patients should be encouraged to attend all activities as usual, despite their fear of panic attacks, so that they do not become phobic. Furthermore, patients should be advised to reduce stress by changing their life-style or by learning stress-management techniques. Patients and their families should be urged to read one of the popular books on panic, such as *The Anxiety Disease*.[11]

Antidepressants

In 1962, imipramine was found to be effective in treating panic disorder.[12] Since then, other tricyclic antidepressants[13] and fluoxetine[14] also have been found to be effective. Interestingly, trazadone[15] and buspirone[16] were found ineffective.

The tricyclics should be the first drugs considered when patients have a concurrent depression in which panic attacks are also present.

The tricyclics should be the first drugs considered when patients have a concurrent major depression in which panic attacks are also present. A patient presenting with panic attacks and a strong personal or family history of depression is often at risk of developing depression later. Patients with a history of alcohol or other drug abuse can take this group of medications without risk of abuse. Patients who want one daily dosing or fear benzodiazepines or MAOIs, may also be good candidates for this group of medications.

Problems with the tricyclic antidepressants include anticholinergic side effects, such as dry mouth, urinary retention, blurry vision, and memory impairment. The antidepressants take up to eight weeks to become optimally effective; patients in a crisis find this delay a major disadvantage. The "jitteriness syndrome"[17] is a frequent and distressing problem for panic patients during the first week or two of treatment, especially with imipramine, desipramine, and fluoxetine. Patients are more anxious, agitated, and sleepless if conventional doses are used. Lower doses decrease this problem but lead to longer waiting periods for relief. The common cardiovascular side effects are tachycardia and orthostatic hypotension. Heart block is a contraindication, and bipolar patients are prone to become manic on an antidepressant. These medications are very toxic when patients overdose, such that 2% to 3% of patients hospitalized from tricyclic antidepressant overdose die.[18] The finding that 20% of panic disorder patients have a history of suicide attempts[19] raises concern about administering these drugs to high-risk patients. The major problem in the present author's experience is noncompliance, because patients find the combination of side effects, transient worsening, and a long wait for improvement to be more than they can tolerate, even with encouragement. Because of all these difficulties with antidepressants, many psychiatrists recommend them only when benzodiazepines are contraindicated or after patients are first stabilized with a benzodiazepine.

Monoamine Oxidase Inhibitors

MAOIs, especially phenelzine, have been found very useful. One major study found that functional impairment improved more on phenelzine than on imipramine or alprazolam.[3] The primary concern is the hypertensive crisis caused by eating one of the forbidden foods or consuming medication that cause this tyramine reaction. Although the dietary limitations can be overcome in well-motivated and reliable patients, the anxiety raised by this group of medication is often a deterrent in patients suffering from fears of catastrophic medical problems. Orthostatic hypotension and mania are potential risks. At this time, most psychiatrists use phenelzine as a backup medication in treating patients who are reliable, especially given the recognition that many patients require long-term pharmacological treatment.

Benzodiazepines

The higher potency benzodiazepines are widely prescribed for panic disorder because they are safe and effective, and provide rapid improvement. A cross-national multicenter study of a large cohort of panic patients[4] demonstrated that alprazolam was effective and that patients showed marked improvement within a week. Alprazolam also reduced anticipatory and general anxiety, enabling patients to overcome their phobic avoidance behaviors more easily. It is extremely safe in overdose when used alone but is dangerous when combined with other sedative-hypnotics or alcohol. Other advantages of alprazolam are its benefits in premenstrual syndrome, which occurs frequently in women with panic attacks, and its relative safety in older patients or those with cardiac problems. Long-term use of the benzodiazepines has been approved by the American Psychiatric Association Task Force on Benzodiazepine Dependence, Toxicity and Abuse, when the drug's benefits outweigh the risks and patients are properly monitored.[20]

Physical dependence is the major drawback of benzodiazepines, but this is rarely a problem when tapering is done slowly and in small decrements. A gradual taper is recommended with all panic medications, as described below. Benzodiazepine abuse is rare in panic patients who are screened for a prior history of substance abuse. The most common side effects of alprazolam are sedation and coordination difficulty, but tolerance tends to develop within a few days and these

problems usually can be completely avoided with low doses and gradual increases. Tolerance to anti-anxiety effects does not develop with time. Most patients require alprazolam four times a day because of its relatively short half-life. Withdrawal symptoms may appear rapidly with missed doses, and interdose rebound may occur because of this rapid metabolism.

Investigators have demonstrated the efficacy of clonazepam,[21] which has the added benefit of a longer half-life than alprazolam but a greater degree of initial sedation. At this time, clonazepam is generally used as a back-up choice for patients who do well on alprazolam, but who metabolize the latter drug so rapidly that more than four doses per day are necessary. Further studies are in progress on this promising benzodiazepine, as well as on lorazepam, in the treatment of panic disorders. The less potent benzodiazepines do not appear to be effective in this disorder except possibly at doses causing excessive side effects. Buspirone, a new non-benzodiazepine anxiolytic, has been found to be ineffective in the treatment of panic disorder.[16]

Table 1. **Pharmacological Treatment of Panic Disorder**

Medication	Starting Dose	Rate of Increase	Usual Daily Dose Range
imipramine (Tofranil) or desipramine (Norpramin)	10 mg hs	Increase by 10mg q4 days until 50 mg; 25 mg q4 days up to 150 mg; then increase by 25mg q3 weeks	150-250mg
nortriptyline (Pamelor)	10mg	Increase by 10mg q4 days until 70 mg; then increase by 25mg q3 weeks	50-150mg
fluoxetine (Prozac)	10mg 1 in AM	Increase to 20mg after 2-4 weeks	20-40mg
phenelzine* (NArdil)	15mg in AM and Noon	Increase by 15mg q3 weeks	45-60mg
alprazolam (Xanax)	.25mg qid	Increase by .25mg/day q3-4 days	2-6mg
clonazepam (Klonopin)	.25mg bid	Increase by .25mg q5-7 days	1.5-4mg

*Dietary and medication contradictions to be followed

Dose Management

The general strategy with all three classes of medication is to start low and increase the dose slowly.

Medication guidelines from the author's experience are listed in Table 1 for the most frequently used antipanic medications. Panic patients tend to be very sensitive to side effects and to increasing anxiety when they experience unusual bodily sensations. It is common to start with pediatric size doses for the first few days and to increase more aggressively after the patient feels comfortable with the medication. The dose generally is increased until the onset of side effects or the elimination of both limited symptom and major panic attacks. Several weeks are required for the antidepressants to become effective; the same conventional doses that are used for treating depression are generally maintained if side effects are tolerable. Serum tricyclic levels may be measured to check compliance or to ensure that the dose is within the usual effective range. These levels have not been validated for panic, so they are only rough guidelines.

The starting dose for alprazolam depends on weighing factors including the urgency of a rapid response and the risk of sedation. Patients unable to work could start with 0.5 mg qid to obtain relief quickly, but working patients would require .25 mg qid in order to help ensure that they not appear sedated. Patients afraid of medication or prone to side effects also would be started on the lower dose. Alprazolam doses can be increased every three to four days, because its antipanic effects are immediate and tolerance to sedation or coordination usually develops within that time frame. Clonazepam doses are generally increased at intervals of five to seven days because of its longer half-life. Patients may continue to have situational or anticipatory anxiety related to places where they most dread having them. It is preferable to use cognitive-behavior therapy for these problems, if possible, rather than only more medication. Patients with any spontaneous, sudden, unexpected panic attacks should continue to increase the dose further unless side effects interfere. Even a 90% reduction in spontaneous panic is insufficient improvement, because the panic patient will continue to fear the next attack and live life defensively. It is important that the physician monitor the patient every week or two in person or by phone as dose increases continue.

Women frequently have a breakthrough panic attack premenstrually that may require an increase in the dose only for that phase of their cycle. Many patients will experience relapses during the first or second month that require a slight increase in the dose, but then no further increases are usually necessary. On the contrary, most patients do not need the original optimal dose after they have been stable for several months and can decrease the dose.

Patients without severe agoraphobia may improve dramatically from medication alone. Without the functional impairment from avoidant behavior, they may feel reassured that they are protected by the medication once they reach an effective dose. If they return to their prior life-style, self-confidence, and sense of well-being, then cognitive or psychodynamic psychotherapy may be unnecessary for these patients.[22]

Tapering from Medication

Generally, a maintenance dose is continued unchanged four to six months or more while the therapeutic homework assignments are undertaken. Once the patient has conquered his or her fears and can go anywhere and do anything while on medication, then the dose can be tapered slowly. Recent studies have demonstrated that panic disorder is often chronic and that many patients who show anxiety symptoms after decreasing a dose are having a relapse of their chronic condition, not withdrawal symptoms.[23,24] These patients require long-term use of medications and become dysfunctional without them. Any of the antipanic medications may be carefully used long-term without harmful consequences.

The decision about when to begin to taper medication is important and psychologically complex. Excessive reliance on medication should be avoided, but patients must feel ready and confident when tapering begins. They should be well informed about their condition and the possibility of either relapse or withdrawal symptoms. They should be back to their baseline level of functioning. Major conflicts and stressors should be resolved, and no foreseeable stressors should be imminent.

The rate of reduction depends on the type of medication and on clinical factors. With tricyclic antidepressants (eg, imipramine), a reduction of 25 mg every two to four weeks is advised. Phenelzine decreases of 15 mg at the same interval are recommended. Alprazolam and clonazepam should be reduced every two weeks for clinical reasons but may be lowered every four days if necessary. Alprazolam is reduced by 0.5 mg if the dose is above 3.0 mg; for doses ranging from 1.0 to 3.0 mg per day, the decrease is by 0.25 mg. Below 1.0 mg daily, the taper is by either 0.25 or 0.125 mg, depending on patient sensitivity to the reductions and their worries about tapering. Clonazepam tapering is by 0.5 mg above 3 mg/day and by 0.25 mg below 3 mg/day. Patients rarely have difficulty during benzodiazepine tapering when reduction is slow and by very small amounts.

Patients without severe agoraphobia may improve dramatically from medication alone. Without the functional impairment from avoidant behavior, they may feel reassured that they are protected by the medication once they reach an effective dose.

Clinical factors influencing the rate of tapering include the duration and intensity of the anxiety problem. For example, patients with 20-year histories of panic attacks and agoraphobia and whose lives have been dramatically improved are reduced monthly, while a patient with a four-month history is tapered weekly. Patients who rush to emergency rooms during each panic attack or who have dependent or histrionic personalities are tapered slowly; patients with excellent family support or a relaxed premorbid baseline may taper relatively quickly. Patients who have completed a cognitive-behavioral treatment reduce medications sooner and more quickly than patients who have relied only on pharmacotherapy. Patients who, at times, experience breakthrough panic attacks reduce either very slowly or postpone reductions. If a patient is at greater risk for a medical problem resulting from panic, such as asthma attack or cardiac arrhythmia, tapering should be more cautious. In patients with a history of alcohol use as a means of treating anxiety, reductions also should be more conservative. Involving the patient in the decision-making regarding tapering is generally helpful and promotes better compliance.

Many factors may lead to the development of anxiety symptoms as the dose is decreased. If the taper is too rapid or the dosage decrease too large, benzodiazepine withdrawal symptoms may occur. These situations are probably much less frequent than previously thought, however. The most frequent etiology of anxiety symptoms is the return of the original panic disorder, which is uncovered during the tapering process when the dose is lowered below the threshold that blocked panic. Use of other drugs, such as caffeine, alcohol or illicit drugs (eg, cocaine or marijuana) may precipitate a panic attack. Women frequently experience an exacerbation of their anxiety attacks premenstrually. Patients may be going through major life stress or have developed a medical problem that was not present at initial evaluation. Occasionally the fear of tapering may cause symptoms.

Because most patients have panic disorder chronically, the goal of the tapering process is to find the lowest effective dose of medication. Although medication sometimes can be eliminated completely, many patients require long-term treatment. Pharmacotherapy is an excellent modality for panic disorder but must be used within the context of an eclectic treatment approach.

Conclusion

Pharmacotherapy is the primary treatment modality for blocking panic attacks. Antidepressants, MAOIs and benzodiazepines each have distinct advantages and disadvantages. They must be initiated, maintained and tapered with care. Physicians are encouraged to become familiar with all of these medications in order to provide patients with treatment that will enable them to lead healthy lives without any limitations from their panic disorder.

References

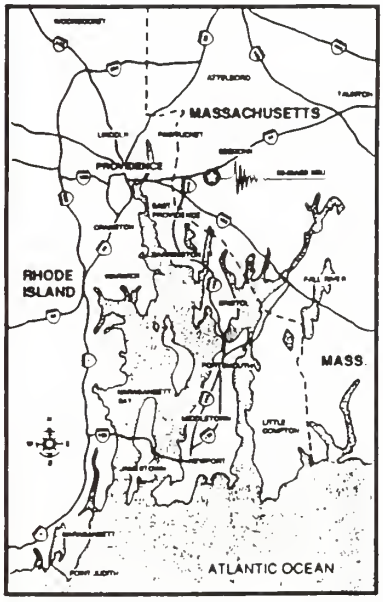
1. Sheehan DV, Soto S. Recent developments in the treatment of panic disorder. *Acta Psychiatrica Scandinavica* 76(suppl 335):75-83, 1987.
2. Klein DF. Importance of psychiatric diagnosis in prediction of clinical drug effects. *Arch Gen Psychiatry* 16:118-126, 1967.
3. Sheehan DV, Ballenger J, Jacobson G. The treatment of endogenous anxiety with phobic, hysterical and hypochondriacal symptoms. *Arch Gen Psychiatry* 37:51-59, 1980.
4. Ballenger JC, Burrows GD, DuPont RL Jr, et al. Alprazolam in panic disorder and agoraphobia: Results from a multicenter trial. I. Efficacy in short-term treatment. *Arch Gen Psychiatry* 45(5):413-422, 1988.
5. Pitts FN Jr, McClure JN Jr. Lactate metabolism in anxiety neurosis. *N Engl J Med* 277:1329-1336, 1967.
6. Woods SW, Charner DS, Lohe J, Goodman WK, Redmond DE Jr, Heninger GR. Carbon dioxide sensitivity in panic anxiety. *Arch Gen Psychiatry* 43:900-909, 1986.
7. Charney DS, Heninger GR, Brier A. Noradrenergic function in panic anxiety: Effects of yohimbine in healthy subjects and patients with agoraphobia and panic disorder. *Arch Gen Psychiatry* 41:751-763, 1984.
8. Charney DS, Heninger GR, Jatlow PI. Increased anxiogenic effects of caffeine in panic disorders. *Arch Gen Psychiatry* 42:233-243, 1985.
9. Reiman EM. The study of panic disorder using positron emission tomography. *Psychiatric Developments* 1:63-78, 1987.
10. Crowe RR. The genetics of panic disorder and agoraphobia. *Psychiatric Developments* 2:171-186, 1985.
11. Sheehan DV. *The Anxiety Disease*. New York: Bantam Books, 1986.
12. Klein DF, Fink M. Psychiatric reaction patterns to imiprimine. *Am J Psychiatry* 119:432-438, 1962.
13. Hollander E, Matterer J, Klein DF. Antidepressants for the treatment of panic and agoraphobia. In Noyes R, Roth M, Burrows GD (eds.) *Handbook of Anxiety*, vol. 4. Amsterdam: Elsevier, 1991.
14. Gorman JM, Liebowitz MR, Fryer AJ, et al. An open trial of fluoxetine in the treatment of panic attacks. *J Clin Psychopharmacology* 7:329-332, 1987.
15. Charney DS, Woods SW, Goodman WK, et al. Drug treatment of panic disorder: The comparative efficacy of imipramine, alprazolam, and trazadone. *J Clin Psychiatry* 47:580-586, 1986.
16. Sheehan DV, Raj AB, Sheehan KH, Soto S. Is buspirone effective for panic disorder? *J Clin Psychopharmacology* 10:3-11, 1990.
17. Pohl R, Yergani V, Balon R, Lycaki H. The jitteriness syndrome in panic disorder patients treated with antidepressants. *J Clin Psychiatry* 49:100-104, 1988.
18. Frommer DA, Kulig KW, Marx JA, Rumack B. Tricyclic antidepressant overdose: A review. *JAMA* 257:521-526, 1987.
19. Weissman MM, Kleman GL, Markowitz JS, Ouellette R. Suicidal ideation and suicide attempts in panic disorder and attacks. *N Eng J Med* 321(18):1209-1214, 1989.
20. American Psychiatric Association Task Force on Benzodiazepine Dependence, Toxicity and Abuse. *Benzodiazepine Dependence Toxicity and Abuse – A Task Force Report of the American Psychiatric Association*. Washington DC: APA, 1990.
21. Spier SA, Pollack MH, Tesare GE, Rosenbaum JF. Clonazepam in the treatment of panic disorder and agoraphobia: A one-year follow-up. *J Clin Psychopharmacology* 6(5):302-304, 1986.
22. Alexander PE, Alexander DD. Alprazolam treatment for panic disorder. *J Clin Psychiatry* 47:301-304, 1986.
23. Alexander PE, Hickey B. Long-term alprazolam treatment of panic disorder. Poster presentation at Anxiety Disorders Association of America, 12th National Conference on Anxiety Disorders, Houston, April 10, 1992.
24. Keller MB. The naturalistic course of anxiety and depressive disorders. Paper presented at the American Psychiatric Association 144th Annual Meeting, New Orleans, May 12, 1991.

Address correspondence to:
Paul E. Alexander, MD
Psychiatric Specialists, Inc.
1145 Main Street
Pawtucket, RI 02860

MAGNETIC RESONANCE IMAGING

RI-MASS MRI

309 Taunton Ave. (Rt 44), Seekonk, MA 02771



- Prompt Scheduling (within 24 hours)
- Pleasant Outpatient Setting
- High Quality Images (Sent to your office within 24 hours.)
- Latest Generation MRI Technology (3D and MR Angiography available)

RI-MASS MRI is a state of the art magnetic resonance imaging facility conveniently located on Taunton Avenue just blocks from the state line. To learn more about RI-MASS MRI or to receive more information about our facility (Rx pads, patient brochures, etc.) please contact Ruth Nash (Site Manager) at **1-800-848-9661.**

Patient Scheduling

1-(800)-848-9661

There's more to Portable X-Ray Service than X-Rays.

Yes, our main business is to provide you with fast, efficient, diagnostic X-Ray services, but we have much more to offer . . . including a staff of people who really care.

- Diagnostic X-Ray Services
- EKG
- Holter-Monitoring*
- Ultrasound Services*
- Same day reporting
- 24 Hour Service
- Seven days a week

*by appointment only

We service the entire Greater Rhode Island area:

- Nursing and Convalescent Homes
- Shut-ins and Private Home Patients
- Post Surgical Patients

PORTABLE X-RAY SERVICE

OF RHODE ISLAND

Certified by the R.I. Department of Health. Reimbursement provided by Medicare, R.I. Blue Shield and Medical Assistance.

100 Highland Avenue Providence, R.I. 331-3996	120 Dudley Street Providence, R.I. 331-3996	154 Waterman Street Providence, R.I. 273-0450	38 Hamlet Avenue Woonsocket, R.I 766-4224

QUESTION:

WHAT ARE THE THREE MOST IMPORTANT THINGS TO CONSIDER WHEN CHOOSING AN INSURANCE AGENCY?

ANSWER:

EXPERIENCE, EXPERIENCE, EXPERIENCE

INSURANCE SINCE 1879

STARKWEATHER & SHEPLEY INC. - (401) 421-6900

Morton Smith, Inc. - (401) 861-6800

155 South Main Street
Providence, Rhode Island 02903

ONLY ONE H_2-ANTAGONIST HEALS REFLUX ESOPHAGITIS AT DUODENAL ULCER DOSAGE. ONLY ONE.

Of all the H_2-receptor antagonists, only Axid heals and relieves reflux esophagitis at its standard duodenal ulcer dosage. Axid, **150** mg b.i.d., relieves heartburn in **86%** of patients after one day and **93%** after one week.[1]

AXID®
nizatidine
150 mg b.i.d.

ACID TESTED. PATIENT PROVEN.

1. Data on file, Lilly Research Laboratories

See accompanying page for prescribing information

© 1991 ELI LILLY AND COMPANY

NZ-2947-B-249304

AXID®
nizatidine capsules

Brief Summary. Consult the package insert for complete prescribing information.

Indications and Usage: 1. *Active duodenal ulcer*—for up to 8 weeks of treatment at a dosage of 300 mg h.s. or 150 mg b.i.d. Most patients heal within 4 weeks.

2. *Maintenance therapy*—for healed duodenal ulcer patients at a dosage of 150 mg h.s. at bedtime. The consequences of therapy with Axid for longer than 1 year are not known.

3. *Gastroesophageal reflux disease (GERD)*—for up to 12 weeks of treatment of endoscopically diagnosed esophagitis, including erosive and ulcerative esophagitis, and associated heartburn at a dosage of 150 mg b.i.d.

Contraindication: Known hypersensitivity to the drug. Because cross sensitivity in this class of compounds has been observed, H_2-receptor antagonists, including Axid, should not be administered to patients with a history of hypersensitivity to other H_2-receptor antagonists.

Precautions: *General*—1. Symptomatic response to nizatidine therapy does not preclude the presence of gastric malignancy.

2. Dosage should be reduced in patients with moderate to severe renal insufficiency.

3. In patients with normal renal function and uncomplicated hepatic dysfunction, the disposition of nizatidine is similar to that in normal subjects.

Laboratory Tests—False-positive tests for urobilinogen with Multistix® may occur during therapy.

Drug Interactions—No interactions have been observed with theophylline, chlordiazepoxide, lorazepam, lidocaine, phenytoin, and warfarin. Axid does not inhibit the cytochrome P-450 enzyme system; therefore, drug interactions mediated by inhibition of hepatic metabolism are not expected to occur. In patients given very high doses (3,900 mg) of aspirin daily, increased serum salicylate levels were seen when nizatidine, 150 mg b.i.d., was administered concurrently.

Carcinogenesis, Mutagenesis, Impairment of Fertility—A 2-year oral carcinogenicity study in rats with doses as high as 500 mg/kg/day (about 80 times the recommended daily therapeutic dose) showed no evidence of a carcinogenic effect. There was a dose-related increase in the density of enterochromaffin-like (ECL) cells in the gastric oxyntic mucosa. In a 2-year study in mice, there was no evidence of a carcinogenic effect in male mice, although hyperplastic nodules of the liver were increased in the high-dose males as compared with placebo. Female mice given the high dose of Axid (2,000 mg/kg/day, about 330 times the human dose) showed marginally statistically significant increases in hepatic carcinoma and hepatic nodular hyperplasia with no numerical increase seen in any of the other dose groups. The rate of hepatic carcinoma in the high-dose animals was within the historical control limits seen for the strain of mice used. The female mice were given a dose larger than the maximum tolerated dose, as indicated by excessive (30%) weight decrement as compared with concurrent controls and evidence of mild liver injury (transaminase elevations). The occurrence of a marginal finding at high dose only in animals given an excessive and somewhat hepatotoxic dose, with no evidence of a carcinogenic effect in rats, male mice, and female mice (given up to 360 mg/kg/day, about 60 times the human dose), and a negative mutagenicity battery are not considered evidence of a carcinogenic potential for Axid.

Axid was not mutagenic in a battery of tests performed to evaluate its potential genetic toxicity, including bacterial mutation tests, unscheduled DNA synthesis, sister chromatid exchange, mouse lymphoma assay, chromosome aberration tests, and a micronucleus test.

In a 2-generation, perinatal and postnatal fertility study in rats, doses of nizatidine up to 650 mg/kg/day produced no adverse effects on the reproductive performance of parental animals or their progeny.

Pregnancy—Teratogenic Effects—Pregnancy Category C—Oral reproduction studies in rats at doses up to 300 times the human dose and in Dutch Belted rabbits at doses up to 55 times the human dose revealed no evidence of impaired fertility or teratogenic effect; but, at a dose equivalent to 300 times the human dose, treated rabbits had abortions, decreased number of live fetuses, and depressed fetal weights. On intravenous administration to pregnant New Zealand White rabbits, nizatidine at 20 mg/kg produced cardiac enlargement, coarctation of the aortic arch, and cutaneous edema in 1 fetus, and at 50 mg/kg, it produced ventricular anomaly, distended abdomen, spina bifida, hydrocephaly, and enlarged heart in 1 fetus. There are, however, no adequate and well-controlled studies in pregnant women. It is also not known whether nizatidine can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. Nizatidine should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nursing Mothers—Studies in lactating women have shown that 0.1% of an oral dose is secreted in human milk in proportion to plasma concentrations. Because of growth depression in pups reared by treated lactating rats, a decision should be made whether to discontinue nursing or the drug, taking into account the importance of the drug to the mother.

Pediatric Use—Safety and effectiveness in children have not been established.

Use in Elderly Patients—Healing rates in elderly patients were similar to those in younger age groups as were the rates of adverse events and laboratory test abnormalities. Age alone may not be an important factor in the disposition of nizatidine. Elderly patients may have reduced renal function.

Adverse Reactions: Worldwide, controlled clinical trials included over 6,000 patients given nizatidine in studies of varying durations. Placebo-controlled trials in the United States and Canada included over 2,600 patients given nizatidine and over 1,700 given placebo. Among the adverse events in these placebo-controlled trials, only anemia (0.2% vs 0%) and urticaria (0.5% vs 0.1%) were significantly more common in the nizatidine group. Of the adverse events that occurred at a frequency of 1% or more, there was no statistically significant difference between Axid and placebo in the incidence of any of these events (see package insert for complete information).

A variety of less common events were also reported; it was not possible to determine whether these were caused by nizatidine.

Hepatic—Hepatocellular injury (elevated liver enzyme tests or alkaline phosphatase) possibly or probably related to nizatidine occurred in some patients. In some cases, there was marked elevation (>500 IU/L) in SGOT or SGPT and, in a single instance, SGPT was >2,000 IU/L. The incidence of elevated liver enzymes overall and elevations of up to 3 times the upper limit of normal, however, did not significantly differ from that in placebo patients. All abnormalities were reversible after discontinuation of Axid. Since market introduction, hepatitis and jaundice have been reported. Rare cases of cholestatic or mixed hepatocellular and cholestatic injury with jaundice have been reported with reversal of the abnormalities after discontinuation of Axid.

Cardiovascular—In clinical pharmacology studies, short episodes of asymptomatic ventricular tachycardia occurred in 2 individuals administered Axid and in 3 untreated subjects.

CNS—Rare cases of reversible mental confusion have been reported.

Endocrine—Clinical pharmacology studies and controlled clinical trials showed no evidence of anti-androgenic activity due to nizatidine. Impotence and decreased libido were reported with similar frequency by patients on nizatidine and those on placebo. Gynecomastia has been reported rarely.

Hematologic—Anemia was reported significantly more frequently in nizatidine than in placebo-treated patients. Fatal thrombocytopenia was reported in a patient treated with nizatidine and another H_2-receptor antagonist. This patient had previously experienced thrombocytopenia while taking other drugs. Rare cases of thrombocytopenic purpura have been reported.

Integumental—Urticaria was reported significantly more frequently in nizatidine- than in placebo-treated patients. Rash and exfoliative dermatitis were also reported.

Hypersensitivity—As with other H_2-receptor antagonists, rare cases of anaphylaxis following nizatidine administration have been reported. Rare episodes of hypersensitivity reactions (eg, bronchospasm, laryngeal edema, rash, and eosinophilia) have been reported.

Other—Hyperuricemia unassociated with gout or nephrolithiasis was reported. Eosinophilia, fever, and nausea related to nizatidine have been reported.

Overdosage: Overdoses of Axid have been reported rarely. If overdosage occurs, activated charcoal, emesis, or lavage should be considered along with clinical monitoring and supportive therapy. The ability of hemodialysis to remove nizatidine from the body has not been conclusively demonstrated; however, due to its large volume of distribution, nizatidine is not expected to be efficiently removed from the body by this method.

PV 2093 AMP [101591]

Additional information available to the profession on request

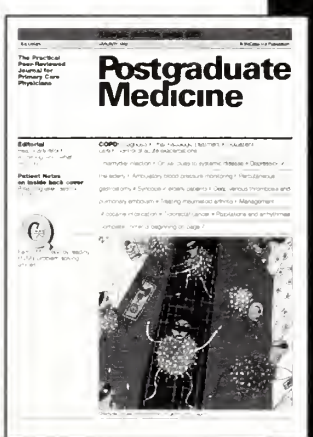
Lilly

Eli Lilly and Company
Indianapolis, Indiana
46285

N7-2947-B-249304

© 1991, ELI LILLY AND COMPANY

US THEM



WHEN YOU NEED TIME ON YOUR SIDE, THE CHOICE IS CLEAR.

NO CLINICAL CLUTTER—PGM ARTICLES ARE CLEAR, CONCISE, WELL ILLUSTRATED, AND PRACTICAL.

Postgraduate Medicine

Panic Disorder: A Clinical Perspective on Acute Treatment and Future Research Needs

Alan Gordon, MD

The diagnosis of panic disorder requires that the individual experience at least one and usually many discrete "attacks" of panic, which are associated with a sudden change to a state of hyperarousal.

Clinical Profile

Fred is a 40-year-old male who currently is diagnosed with panic disorder with agoraphobia, coupled with one previous episode of alcohol dependence. Fred's first attack was unexpected and was not triggered by external concerns; Fred was 35 when this occurred. The attack was characterized by the following symptoms: dizziness, palpitations, trembling, nausea, depersonalization, paresthesias, hot flashes, fear of dying, and the fear of going crazy. Initially the attacks occurred as frequently as four times a week. Fred noted that although the actual number of attacks gradually decreased, the fear of having an attack remained. No organic factor could be attributed as the cause of these attacks.

With the onset of frequent attacks Fred also experienced agoraphobia. The first attack marked the beginning of persistent fear which Fred labeled, "anticipatory anxiety." His overwhelming anxiety prompted him to leave his place of work; he was unemployed for three years. Fred would not leave his home, nor would he answer the door or phone. Thus complete avoidance of all outside contact lasted four months, at which point Fred sought the help of a clinician.

Fred made numerous attempts at seeking treatment (psychotherapist, general practitioner, psychiatrist, sports doctor); currently he sees a psychiatrist for medication (Pamelor, Xanax, and Inderal). He was hospitalized once for psychiatric evaluation.

It should be noted that Fred experienced a year-long period of alcohol dependence. This onset while he was housebound and continued until he found an effective treatment plan.

Currently Fred is employed and taking graduate level coursework. Although Fred maintains a fairly rigorous routine, he always checks to ascertain easy escape routes in any given situation, and avoids situations in which he would not be in control (ie, he drives the car, but refuses to be a passenger). He continues to experience one to three attacks per week; but he labels them as "less intense and manageable".

Panic disorder is now recognized as a disorder, separate and apart from generalized anxiety disorder. In the past decade there has been much research on treatments for this disorder.

In order to select the correct treatment protocol, it is important to draw a clear distinction between generalized anxiety disorder, panic disorder and phobias. Generalized anxiety disorder refers to a state of generalized autonomic hyperactivity and motor tension, whereas the diagnosis of panic disorder requires that the individual experience at least one and usually many discrete "attacks" of panic. These panic attacks are associated with a sudden change to a state of hyperarousal, and the individual usually experiences an intense sense of fear or discomfort. These episodes typically peak within minutes and subside within 10 to 20 minutes. The initial attack(s) is, by definition, spontaneous in that no identifiable trigger can be identified. The place of first occurrence often becomes associated with panic attacks leading to phobic avoidance of similar

Alan Gordon, MD, is Clinical Associate Professor, Department of Psychiatry and Human Behavior, Brown University, Providence, Rhode Island, and Coordinator, Panic Disorder Program, Butler Hospital, Providence, Rhode Island.

ABBREVIATIONS USED:

EEG: electroencephalogram
NIH: National Institutes of Health

situations. Other situations that are associated with a feeling of being trapped, or preventing the individual from rapidly accessing help, or placing them at risk for public humiliation are commonly avoided. Apprehension of having further attacks frequently results in a comorbid generalized anxiety disorder, as well as secondary panic attacks, triggered by exposure to situations associated with previous spontaneous attacks.

Thus, a vicious cycle of panic attacks, generalized anxiety and phobic avoidance can be set in motion. Agoraphobia without panic disorder is uncommon.

Treatment planning is best formulated by conceptualizing the different stages of the illness.

Differential Diagnosis with Non-psychotic Medical Illness or the First Step in the Treatment of Panic Attacks

Because panic attacks are associated primarily with discrete bursts of autonomic nervous system hyperactivity, it is important first to exclude any somatic disorder or drug disorder that may be causing the attacks. Common conditions that have been associated with panic disorder include hyperthyroidism, diabetes, inner ear pathology, arrhythmias, in particular supraventricular tachycardia, mitral valve prolapse and seizure disorders. The accompanying article by Goldberg, in this issue of *Rhode Island Medicine,* elaborates on the appropriate medical differential diagnosis.

Apprehension of further attacks results in a comorbid generalized anxiety disorder, as well as secondary panic attacks, triggered by exposure to situations associated with previous spontaneous attacks.

It is, therefore, important to take a careful history and perform a focused physical exam, with laboratory screening and EKG to rule out these conditions. It may be argued that an EEG should also be part of the screening protocol.

While these screening investigations are important, their yield is not usually very high, so it is important to make the provisional diagnosis early and begin treatment before extensive special investigations are ordered. Failure to do this has led to an extraordinary overutilization of medical services with its incumbent financial burden. At the same time, the patient is exposed to prolonged duress and frequent humiliation, as his or her profound distress continues to evade confirmation and tends to be underestimated.

At a recent NIH Consensus Development Conference, there was no consensus about whether cognitive, behavioral or pharmacologic treatments were the best treatment approaches. The panel reached agreement only on the apparent efficacy of both cognitive and pharmacological treatments.

The argument for first considering non-pharmacologic treatment modalities has much appeal. If the individual is able to develop a sense of mastery or control over these attacks, this can provide the greatest protection against further attacks. Commonly used strategies include distraction techniques, autosuggestion and exercises to increase control of breathing and skeletal muscle tone. After becoming sensitized to panic attacks, a state of hyperarousal does appear to produce "kindling," which has the effect of lowering the threshold for further panic attacks. Relaxation exercises may be helpful in decreasing arousal.

Most patients who present for treatment in the acute phase are far too distressed to utilize these techniques effectively without pharmacological treatments. Barlow has reported comparable results using only cognitive behavioral techniques.[1] However, this requires that the patient demonstrate focus, discipline and motivation, which are frequently lacking during the acute phase. This may suggest a natural selection process for patients who may complete cognitive behavioral protocols successfully.

Treatment of Panic Attacks During the Maintenance Phase

The research on the natural history of panic disorder to date has suggested that panic disorder patients presenting for treatment have been continuously ill with high rates of recurrence and relapse, usually over a decade. This finding implies, as does the experience of most clinicians, that many patients have a chronic and continuous course and, therefore, need long-term treatment.

After the acute panic attacks have been stabilized, it is important to continue maintenance therapy and recognize when it is appropriate to taper medication.

Most research to date has suggested that panic disorder patients presenting for treatment have been continuously ill for a long time with high rates of recurrence and relapse, usually over a decade.

Panic attacks frequently are associated with a state of generalized anxiety, hypochondriasis and a feeling of loss of control, as described in the clinical profile of Fred. Cognitive behavioral techniques have an important role to play in reducing these manifestations and increasing the patient's sense of self-mastery.

Psychoeducation is an integral part of treatment, since it is important for the patient to recognize that this is a common disorder that is responsive to treatment. It is important to reinforce that no matter how out of control one might feel during an attack, it is time-limited and not life-threatening or associated with other catastrophic consequences. For example, Fred reports a degree of frustration; he feels panic disorder has significantly limited his career success. However, he feels his current treatment plan, and his insight

into his disorder, has enabled him not only to leave the house, but also to manage the stress of a full-time job and graduate school.

Cognitive behavioral training using distraction techniques and autosuggestion can increase again the individual's sense of control over physiologic responses. More recently treatments with the goal of reducing panic attacks directly have been developed. Relaxation training can be helpful in reducing general arousal, which will raise the threshold for further panic attacks.

While mastery of these techniques undoubtedly reduces and may even eliminate the need for maintenance medication, they are not practiced frequently by psychiatrists. This may, be due, in part, to a general lack of experience in using these techniques. The time and cost required for patients to learn these techniques is frequently unattractive to them after they have achieved a good response to pharmacologic treatments. Not surprisingly, other mental health professionals have concentrated on these therapies.

There is clearly a need for more psychiatrists to learn cognitive and behavioral therapies and to cooperate with other professionals who have these skills.

Treatment of Phobic Avoidance

The avoidant behavior of agoraphobics is usually related to the fear of having panic attacks in situations where help is not readily available, or loss of control may lead to public humiliation. This appears to be primarily a learned response and is best treated with cognitive behavioral techniques.

An emphasis on in vivo desensitization is particularly important. It is important to take into account personality variables that may interfere with treatment, and at times, psychotherapy dealing with resistance to treatment may be necessary. An evaluation of the patient's family system is helpful, since family members may be supporting avoidant behavior or may be exasperated and/or undermining the patient's efforts. It has also been suggested that higher doses of alprazolam and imipramine may result in reductions in phobic behavior.

Summary

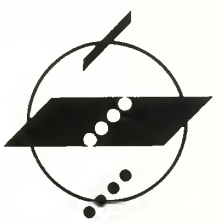
Panic disorder is a common disorder for which there are highly effective treatments. Patients usually present for treatment in acute distress and initially have difficulty responding to cognitive behavioral therapies. In contrast there is a high response rate to pharmacologic treatments. Cognitive behavioral techniques can be helpful in facilitating the taper and eventual discontinuation of medication and may play a role in preventing relapse. The disorder appears to have a chronic course requiring maintenance medication for at least six months. Phobic avoidance appears to be primarily a learned response and is best treated with in vivo desensitization.

References

1. Barlow DH. Long-term outcome for patients with panic disorder treated with cognitive-behavioral therapy. *J Clin Psychiatry* 51:12 (suppl A), 1990.
2. Ballenger JC. Long-term pharmacologic treatment of panic disorder. *J Clin Psychiatry* 52:2(suppl), 1991.

Address correspondence to:
Alan Gordon, MD
Butler Hospital
345 Blackstone Boulevard
Providence, RI 02906

RHODE ISLAND COMPUTERIZED IMAGING, INC.



Cat Scan Facility
401•751•1110

weekdays
7 am - 5 pm

- Evening appointments for contrast studies
- Medicare, Ocean State
  Rhode Island Blue Cross/Blue Shield approved
- Board Certified Radiologist

Located in: Atwood Medical Center
Suite LL3
1524 Atwood Avenue
Johnston, RI 02919

Medical Aspects of Panic Disorder

Richard J. Goldberg, MD

Panic attacks may be due to one or more of a large number of underlying physical or psychiatric disorders. Only when these possible etiologies have been excluded may the diagnosis of panic disorder be established.

Panic attacks are periods of abrupt onset of intense fear or anxiety accompanied by a number of physical symptoms. Panic attacks may be due to many underlying physical or psychiatric disorders (see Table 1). Only when these possible etiologies have been excluded may the diagnosis of panic disorder be established using the guidelines outlined in this issue of *Rhode Island Medicine*.

While exhaustive medical diagnostic testing is neither desirable nor cost-effective for every patient with severe episodic anxiety, the clinician must be aware of the medical differential diagnosis and should pursue reasonable possibilities by a thorough history, review of systems, and pertinent laboratory testing. The purpose of the first part of this review is to survey the medical disorders that may account for panic attacks.

Richard J. Goldberg, MD, is Psychiatrist-in-Chief, Rhode Island Hospital and Women & Infants Hospital, Providence, Rhode Island, and Professor, Department of Psychiatry and Human Behavior, and Department of Medicine, Brown University, Providence, Rhode Island.

Since the somatic and autonomic presentations of panic disorder may mimic a number of other medical conditions convincingly, the second part of this review will survey the various medical presentations of panic disorder.

Medical Disorders Presenting as Panic Attacks

Effects of Drugs

The toxic and withdrawal effects of drugs always need to be considered as a potential cause of panic symptoms. Any patient considered to have a diagnosis of panic disorder should have a carefully assembled list of all substances inhaled, ingested, or injected during the previous month. If there is any doubt about what drugs the patient has been taking, a toxicology screen should be obtained. Such screening is especially useful when the patient is suspected of surreptitious drug use. A drug history should include over-the-counter medications and occupational exposures. Each substance, in terms of its potential to cause anxiety, should be reviewed.[2]

Caffeine. Caffeine is one of the most widely used psychotropic drugs in the United States and is found in coffee, tea, soda, and a variety of over-the-counter medication combinations. The approximate amount of caffeine in a cup of coffee is 100 mg to 150 mg. While individual sensitivity varies, symptoms of caffeinism that may occur at doses of only 200 mg are identical to the classic description of an anxiety episode.[3] Caffeine may precipitate an actual panic attack in patients with that underlying diagnosis.[4] In chronic users, caffeine abstinence should also be considered as a possible source of intermittent anxiety.[5]

Cocaine. Symptoms of panic/anxiety may appear soon after the initial euphoriant effects of cocaine.[6] Cocaine has been reported to induce panic attacks and may precipitate panic disorder that continues autonomously even after the cocaine use is discontinued.[7] The wide availability of "crack," a form of cocaine that is readily smoked

ABBREVIATIONS USED:

MVP: Mitral valve prolapse
HVS: Hyperventilation syndrome
DTs: Delirium tremens
CNS: Central nervous system
GTT: Glucose tolerance test
EEG: Electroencephalogram
MMPI: Minnesota Multiphasic Personality Inventory

leading to higher and more intense effects, has led to more dangerous symptoms including hyperpyrexia, seizures, and ventricular arrhythmias.[8] Urine tests can confirm cocaine use in cases where the patient's story is ambiguous. Detectable amounts of cocaine are found in the urine or plasma for only a few hours after use, though one of the metabolites, byzoylecgonine, may be detected in a urine sample for as long as 48 hours after use.[9]

Alcohol and Sedatives. Alcohol withdrawal is a frequent etiology for symptoms of panic.[10] Minor abstinence syndrome, which has its modal onset about 24 hours after cessation of drinking, presents with anxiety and tremulousness (the "shakes" and insomnia) and is a self-limited syndrome resolving over several days. While the patient with minor abstinence syndrome may have discomfort and complain of anxiety, the major concern for the physician is whether such symptoms are the harbinger of major abstinence syndrome, delirium tremens (DTs). In the patient with major abstinence, anxiety and tremulousness are accompanied by symptoms of autonomic arousal including tachycardia, mydriasis, diaphoresis, and increased temperature. The syndrome of major abstinence from alcohol may be duplicated by withdrawal from any CNS sedative such as benzodiazepines (especially those with shorter half-life) or barbiturates. The time of onset and severity of the withdrawal symptoms are related to the half-life of the sedative in question. Drugs with short half-lives have more rapid onset of major abstinence and more severe withdrawal symptoms, often including seizures. Concurrent medication use may mask the classic presentation of sedative withdrawal. Specifically, beta-blockers may prevent tachycardia and tremor while narcotics may prevent the development of mydriasis.

Opiates. Narcotic abstinence is always accompanied by anxiety. In the hospital, patients may be undergoing narcotic withdrawal because of street addictions prior to admission or because of iatrogenic causes, such as the abrupt lowering of dose often seen on surgical services. Iatrogenic withdrawal may occur when patients are changed from parenteral to oral narcotics without consideration of differences in oral/parenteral ratios. Therefore, the anxious patient who has just had a change from parenteral to oral narcotics is likely to be anxious because of increased pain due to inadequate medication or to withdrawal effects.

Alpha adrenergic stimulants. These agents, used in over-the-counter

Table 1. **Medical Disorders Producing Anxiety**

Cardiovascular
- Angina pectoris
- Cardiac arrhythmias
- Congestive heart failure
- Hypertension
- Hypotension
- Mitral valve prolapse
- Pulmonary emboli

Drug-Related
- Anti-cholinergic toxicity
- Baclofen (Lioresal)
- Bromocriptine
- Calcium channel blockers
- CNS sedative withdrawal (eg, alcohol, benzodiazepines)
- Cycloserine (Seromycin)
- Hallucinogens
- Indomethacin (Indocin)
- L-dopa
- Neuroleptics (akathisia may simulate anxiety)
- Opiate withdrawal
- Oxymetrazoline (Afrin)
- Quinacrine (Atabrine)
- Stimulants (eg, amphetamine, cocaine)
- Sympathomimetics (eg, isoetharine, isoproterenol, terbutaline)
- Xanthines (eg, caffeine, theophylline)

Electrical
- Complex partial seizures

Metabolic
- Carcinoid syndrome
- Hypercalcemia
- Hypercortisolemia
- Hyperkalemia
- Hyperthyroidism
- Hypoglycemia (drug-induced, fasting, malabsorptive, postprandial)
- Hyponatremia
- Hypoxia (asthma, chronic obstructive pulmonary disease, hypovolemia, pneumonia, pneumothorax, pulmonary edema)
- Hypoparathyroidism
- Pheochromocytoma
- Porphyria

Neurologic
- Encephalopathies
- Essential tremor
- Postconcussion syndrome

decongestants, include phenylpropanolamine, ephedrine, phenylephrine, and pseudoephedrine. These drugs are closely related to amphetamines and can produce symptoms of anxiety, restlessness, irritability, insomnia, hypertension, tachyarrhythmias and seizures.[11]

The syndrome of major abstinence from alcohol may be duplicated by withdrawal from any CNS sedative such as benzodiazepines (especially those with shorter half-lives) or barbiturates.

Bronchodilators. These chemically resemble the catecholamines, including isoetharine, isoproterenol, epinephrine, metaproterenol, and albuterol. These drugs have peripheral effects that include increased heart rate, elevated blood pressure, and elevated lactate levels, all of which can contribute to feelings of anxiety. Systemic effects, reported even with metered-dose inhalers,[12] include symptoms of anxiety, restlessness, nervousness, tremor, irritability, insomnia, and emotional lability.

Theophylline. Theophylline is a methylxanthine, related chemically to caffeine, which is capable of producing powerful cardiovascular effects with tachycardia along with nervousness and anxiety states.[13] The pulmonary patient who develops anxiety attacks often is manifesting symptoms from a combination of factors including hypoxia, high doses of beta adrenergic agonists, and excessive levels of theophylline. Theophylline plasma levels always should be checked in such patients and brought down to the lowest level possible that is compatible with the patient's medical management.

Calcium channel blockers. This group, which includes verapamil, nifedipine, and diltiazem has been reported to produce neuropsychiatric symptoms that include anxiety, tremulousness, jitteriness, and sleep disturbance.[14-16]

Nicotine. Nicotine withdrawal has been noted to lead to the onset of panic attacks, which remitted when nicotine use was resumed.[17] In general, nicotine has been reported to have both calming as well as arousing effects, depending on a variety of factors. In dealing with patients who attempt to quit smoking, the emergence of extreme anxiety, including panic attacks, is a possibility that should be anticipated.[18]

Other drugs reported to produce anxiety as a side effect include amphetamine and similar anorexic agents, antihistamines, baclofen, cycloserine, indomethacin, oxymetazoline, quanicrine, estrogen and propranolol. [2,19,20]

Specific Medical Disorders

Hypoglycemia. Wide and abrupt fluctuation in plasma insulin levels may lead to profound hypoglycemia as a cause of anxiety and panic states. Endogenous hypoglycemia, which can be a eureactive response to carbohydrate ingestion, can be precipitated in rare cases by an insulinoma. Exogenous causes of hypoglycemia include excessive insulin or oral hypoglycemic use that is iatrogenic, inadvertently or purposefully, Hypoglycemia also may be precipitated by a number of drugs including salicylates, antihistamines, monoamine oxidase inhibitors, propranolol, phenylbutazone, alcohol, phenytoin and estrogens.

Reactive (postprandial) hypoglycemia with sudden onset of anxiety occurs three to four hours after eating, with symptoms resulting from an exaggerated and asynchronous physiologic response to carbohydrate ingestion. Clinically significant hypoglycemia is associated with a variety of neuroendocrine responses including increased serum cortisol along with symptoms such as sympathetic autonomic arousal, anxiety, irritability, sweating, tremulousness, and tachycardia. Episodes of reactive hypoglycemia do not show the progression of frequency or severity that is characteristic of insulinoma.[21] When reactive hypoglycemia is suspected on the basis of characteristic symptom, the appropriate diagnostic evaluation is a properly performed five-hour glucose tolerance test (GTT).[22] Anxious patients often feel that hypoglycemia accounts for their symptoms; however, there is scant documentation of psychiatric symptoms as direct consequence of low blood sugar.[23,24] However, patients who have had gastrectomy, gastrojejunostomy, or vagotomy and pylorplasty have a much higher incidence of reactive hypoglycemia than normals,[25,26] with high insulin levels about one-half hour after feeding.

. . . the anxious patient who has just had a change from parenteral to oral narcotics is likely to be anxious because of increased pain due to inadequate medication or to withdrawal effects.

Complex Partial Seizures. Panic is the most common ictal emotion associated with temporal lobe epilepsy.[27] Anxiety has been reported as a feature of temporal lobe epilepsy secondary to tumor.[28] In general, anxiety as an aspect of epilepsy should be considered when it occurs in the context of other classical features of complex partial seizures (such as autonomic symptoms, motor automatisms, perceptual distortions, or disturbances in the subjective sense of reality). In addition, the likelihood of complex partial seizures is increased if the patient has a history of head injury, febrile convulsions in childhood, birth trauma, personal or family history of seizures, or history of encephalitis.

The characteristic abnormality in temporal lobe seizure is the anterior temporal spike focus; however, in the waking state at least one half of patients have normal EEGs.[29] A sleep record does increase the likelihood of detecting abnormal EEGs in epileptic patients, although the percent of false negatives remains about 30% to 40%. The use of special electrode place-

ments such as nasopharyngeal leads and especially the use of continuous ambulatory EEG monitoring[30,31] can increase the diagnostic yield. At times, anticonvulsant trials may be indicated for patients with refractory panic attack in whom an unequivocal diagnosis of epilepsy cannot be made.[32]

Angina Pectoris. Angina patients may experience episodes of dypsnea and palpitations accompanied by only mild chest discomfort, which can suggest anxiety rather than angina. When such episodes are precipitated by exercise or emotional stress, angina should be considered and cardiac evaluation performed, especially in patients over 40 or those with a cardiac history.

Cardiac Arrhythmias. This condition may produce palpitation, dypsnea, and light-headedness that can be mistaken for a panic attack. For this reason, pulse regularity should always be checked during a panic attack. If the diagnosis of arrhythmia is suspected, Holter monitoring may be helpful in confirming the diagnosis. For those patients with arrhythmias, a host of medical conditions that are also associated with anxiety symptoms need to be considered, such as hyperthyroidism, caffeinism, or nicotine abuse.[33]

Recurrent Pulmonary Emboli. This condition may present as repeated episodes of acute anxiety associated with hyperventilation and dypsnea.[34] Arterial blood gases may reveal decreased oxygen during an episode, though the confirmatory test of most use is the ventilation-perfusion lung scan. This diagnosis should be considered in those patients who have some predisposition such as hyperviscosity, prolonged bed rest, peripheral venous thrombosis, or recent pelvic surgery.

Hyperthyroidism. Hyperthyroidism usually presents with symptoms of nervousness, palpitations, diaphoresis, heat intolerance and diarrhea.[35] Signs include tachycardia, tremor, weight loss, and hot, moist skin. A thyroid function screen should be part of the evaluation of patients with panic attacks. MacCrimmon, Wallace, Goldberg and Streiner (1979) compared the MMPI scores of hyperthyroid patients with those of normal subjects and found that the hyperthyroid patients produced a typical "aneurotic" pattern, which returned to normal after successful treatment of the hyperthyroidism.[36]

Pheochromocytoma. This is a rare disorder involving catecholamine secretion by a tumor of the renal medulla. The output of catecholamines may be episodic or continuous, producing acute or chronic symptoms of anxiety, often accompanied by headache and flushing.[37] Hypertension is usually present during acute episodes, and 60% to 80% of patients have sustained hypertension. In one study of 17 patients with active pheochromocytoma,[38] none experienced the severe apprehension or fear characteristic of panic attacks. One patient received a diagnosis of possible panic disorder, two met criteria for generalized anxiety disorder, and two met criteria for major depressive episode. Therefore, there does not appear to be a strict and predictable relationship between the presence of catecholamine secreting tumors and severe anxiety.

. . . anxiety as an aspect of epilepsy should be considered when it occurs in the context of other classical features of complex partial seizures.

Hypoparathyroidism. This condition may present with a wide range of psychiatric disorders including anxiety as the primary symptom in about 20% of the cases.[39] Hypoparathyroidism should be suspected in patients who have had thyroid surgery because of the possibility of inadvertent damage to the parathyroids. It also should be considered in patients with hypocalcemia and hyperphosphatemia in the presence of normal renal function. Parathormone assays usually will be depressed.

Mitral Valve Prolapse (MVP). Some studies have shown that patients with panic disorder have a higher incidence of MVP than psychiatrically normal people, while other studies have failed to document this increased prevalence, possibly because of differences in the stringency of criteria used for the diagnosis of MVP.[40-42] About half of patients with MVP, at some time, complain of palpitations and a form of cardiac rhythm disturbance.[43] Further, a study of the prevalence of anxiety disorder in patients with MVP found no differences between patients and controls, casting further doubt on the etiologic role of MVP in panic attacks.[44] While there continues to be support for some relationship between MVP and panic attacks, there is no evidence that MVP causes panic attacks.[45,46]

Hyperventilation Syndrome (HVS). This syndrome has been described in the literature for more than 40 years.[47,48] Anxiety is a cardinal symptom along with a variety of other medical symptoms including faintness and visual disturbances, nausea, vertigo, headache, palpitations, dypsnea, diaphoresis, and paresthesia. The diagnosis of HVS has been made on the basis of the patient's response to overbreathing (breathing by mouth for up to three minutes or until dizzy). If the symptoms in question are entirely reproduced without an alternative explanation by physical examination, medical history, or laboratory tests, the diagnosis can be established.

Hyperventilation leads to excessive elimination of CO_2, acute respiratory alkalosis, and cerebral artery constriction. In 240 seconds of overbreath, cerebral blood flow can be reduced by 40%, which is the cause of EEG slowing that often accompanies hyperventilation.[49,50] Muscular tension is heightened by a decreased ionization of calcium associated with the increase in pH.[51] Hyperventilation also causes increased coronary artery resistance and may result in chest discomfort that is difficult to distinguish from angina pectoris, along with nonspecific downward depression of the ST segment and T-wave flattening.[52,53] Unlike ischemic ST changes, those caused by hyperventilation usually appear early during exercise and tend to disappear

as exercise continues.[54] It is likely that many cases of HVS are actually panic disorder presenting with a prominent respiratory symptom component.

Post-concussion Syndrome. Cerebral concussion classically is regarded as a disorder that produces no irreversible anatomic lesions. Clinically, concussion results in an instantaneous diminution of function or loss of consciousness followed by a rapid and complete recovery. The episode may be surrounded by a sphere of amnesia that rapidly shrinks to a finite minimum including about one-tenth of the total as retrograde amnesia.[55] For most patients, the symptoms abate for a few weeks to a few months. However, it has been estimated that 20% of head injuries involving no demonstrable damage lead to a syndrome involving medically unexplained symptoms, with anxiety as one of the most frequent disabling symptoms.[56] The post concussion syndrome typically consists of anxiety, impairment of sleep and appetite, irritability, light-headedness, headaches, and poor concentration.

Symptoms that follow concussion may be a direct result of neuronal damage and alteration of cerebral blood flow resulting in regional and generalized abnormalities correlating with the presence of psychological symptoms and impaired information processing.[57-59]

Medical Presentation of Panic Disorder

Panic disorder is notable among the anxiety disorders for presenting of episodic physical symptoms that may not quite fit into a typical medical diagnosis. The broad range of physical symptoms by which panic disorder can present includes dypsnea, palpitations, chest pain or discomfort, choking or smothering sensation, dizziness, paresthesia, hot and cold flashes, sweating, faintness, and trembling or shaking.

The diagnosis of panic disorder is often overlooked. Sheehan (1982) has pointed out that, because of the wide variety of variable physical symptoms associated with panic disorder, it is one of the great imposters in medical practice.[60] Panic disorder is associated with a high rate of medical utilization.[61] In one series, all patients with panic disorder had previously consulted a physician and 70% had consulted more than 10 physicians.[62] In another retrospective study of 55 patients with panic disorder referred by primary care physicians to psychiatrists, 89% initially presented with one or two somatic symptoms, and misdiagnosis often continued for months to years.

. . . it has been estimated that 20% of head injuries involving no demonstrable damage lead to a syndrome involving medically unexplained symptoms, with anxiety as one of the most frequent disabling symptoms.

Katon (1984, 1990) has reported that the three most common presentations of panic disorder are cardiac symptoms (chest pain, tachycardia, irregular heart beat), gastrointestinal symptoms (especially epigastric distress), and neurologic symptoms (headache, dizziness/vertigo, syncope, or paresthesias).[63,64] Eighty-one percent of patients had a presenting pain complaint. Hypertension and peptic ulcer were the most commonly associated medical diagnoses and depression and alcoholism the most frequently associated psychiatric diagnoses. A recent study found the prevalence of panic disorder in an ambulatory cardiology practice to be over 9%.[65]

Conclusion

The physical manifestations of panic disorder can be very convincing for some underlying medical diagnosis, leading to repeated negative medical workups and treatments. In cases of recurrent, episodic, medically unexplained physical symptoms, panic disorder should be considered as possible explanation. In such cases, a trial of antipanic medication, following the guidelines in this issue of *Rhode Island Medicine*, may be helpful both diagnostically and in terms of patient management.[66]

References

1. White K. Anxiety disorders: An overview. *RI Medicine* 75:241-244, 1992.
2. Abramowicz M. Drugs that cause psychiatric symptoms. *The Medical Letter* 3, 1989.
3. Victor BS, Lubetsky M, Greden JF. Somatic manifestations of caffeinism. *J Clin Psychiatry* 42:185-188, 1981.
4. Charney DS, Heninger GR, Jatlow PI. Increased anxiogenic effects of caffeine in panic disorders. *Arch Gen Psychiatry* 42:233-243, 1985.
5. White BC, Lincoln CA, Pearce NW, Reeb R, Vaida C. Anxiety and muscle tension as consequences of caffeine withdrawal. *Science* 209:1547-1548, 1980.
6. Resnick RB, Kestenbaum RS, Schwartz LK. Acute systemic effects of cocaine in man: A controlled study by intranasal and intravenous routes. *Science* 195:696-698, 1976.
7. Aronson TA, Craig TJ. Cocaine precipitation of panic disorder. *Am J Psychiatry* 143:643-645, 1986.
8. Abramowicz M. Crack. *The Medical Letter*, 28:69-70, 1986.
9. Wilkerson P, Van Dyke C, Jatlow P, Barash P, Byck R. Intranasal and oral cocaine kinetics. *Clin Pharmacol Ther* 27:386-394, 1980.
10. Lerner WD, Fallon HJ. The alcohol withdrawal syndrome. *N Engl J Medicine* 313:951-952, 1985.
11. Pentel P. Toxicity of over-the-counter stimulants. *JAMA* 252:1898-1903, 1984.
12. Harris MC. The use and abuse of pocket nebulizers in the treatment of asthma. *Postgraduate Medicine* 23:170-173, 1958.
13. Jacobs MA, Senior RM, Kessler G. Clinical experience with theophylline: Relationship between dosage, serum concentration, and toxicity. *JAMA* 235:1983-1986, 1976.
14. Bela SV, Raftery EB. The role of verapamil in chronic stable angina. A controlled study with computerized multistage treadmill exercise. *Lancet* 1:841-844, 1980.
15. Mueller HS, Chahine RA. Interim report of multicenter double-blind placebo-controlled studies of nifedipine in chronic stable angina. *Am J Med* 71:645-657, 1981.
16. Rinkenberger RL, Psystowksy EN, Heger JJ, Troup PJ, Jackman WM, Zipes DP. Effect of intravenous and chronic oral verapamil administration in patients with supra-ventribular arrhythmias. *Circulation* 62:996-1010, 1980.

[17] Brodsky L. Can nicotine control panic attacks? *Am J Psychiatry* 142:524, 1985.
[18] Hughes JR, Gust SW, Skoog K, Keenan RM, Fenwick JW. Symptoms of tobacco withdrawal. *Arch Gen Psychiatry*, 48:59, 1991.
[19] Price WA, Heil D. Estrogen-induced panic attacks. *Psychosomatics* 29:433-435, 1988.
[20] Levinson DF, Acquaviva J. Exacerbation of panic disorder during propranolol therapy. *J Clin Psychopharm* 8:193-195, 1988.
[21] Freinkel N, Metzger BE. Oral glucose tolerance curve and hypoglycemias in the fed state. *N Eng J Med* 280:820-828, 1969.
[22] Anderson RW, Lev-Ran A. Hypoglycemia: The standard and the fiction. *Psychosomatics* 26:38-47, 1985.
[23] Gorman JM, Martinez JM, Liebowitz MR, Fyer AJ, Klein DF. Hypoglycemia and panic attacks. *Am J Psychiatry* 141:101-102, 1984.
[24] Uhde TW, Vittone BJ, Post RM. Glucose tolerance testing in panic disorder. *Am J Psychiatry* 141:1461-1463, 1984.
[25] Breurer RI, Moses H, III, Hagen TC, Zuckerman L. Gastric operation and glucose homeostasis. *Gastroenterology* 62:1109-1119, 1972.
[26] Haflen L, Leichter S, Reich T. Organic brain dysfunction as a possible consequence of post-gastrectomy hypoglycemia. *Am J Psychiatry* 132:1321-1324, 1975.
[27] Weil AA. Ictal emotions occurring in temporal lobe dysfunction. *Arch Neur* 1:87-97, 1959.
[28] Dietch JT. Cerebral tumor presenting with panic attacks. *Psychosomatics* 25:861-863, 1984.
[29] Gibbs FA, Gibbs EC. *Atlas of Electroencephalography* (Vol 2) Cambridge MA: Addison-Wesley, 1952.
[30] Kristensen O, Sendrup EH. Sphenoidal electrodes. *Acta Neurologica Scandinavica* 58:157-166, 1978.
[31] Lieb JP, Walsh GO, Babb TL, Walter RD, Crandall PH. A comparison of EEG seizure patterns recorded with surface and depth electrodes in patients with temporal lobe epilepsy. *Epilepsia* 17:137-160, 1976.
[32] McNamara ME, Fogel BS. Anticonvulsant-responsive panic attacks with temporal lobe EEG abnormalities. *J Neuropsychiatry* 2:193-196, 1990.
[33] Lynch JJ, Paskewitz DA, Gimbel KS, Thomas SA. Psychological aspects of cardiac arrhythmia. *Am Heart J* 93:645-657, 1977.
[34] Ferrer M. Mistaken psychiatric referral of occult serious cardiovascular disease. *Arch Gen Psychiatry* 18:112-113, 1968.
[35] Hall RCW. Psychiatric effects of thyroid hormone disturbance. *Psychosomatics* 24:7-18, 1983.
[36] MacCrimmon DJ, Wallace JE, Goldberg WM, Streiner DL. Emotional disturbance and cognitive deficits in hyperthyroidism. *Psychosomatic Med* 41:331-340, 1979.
[37] Lishman WA. Endocrine disorders and metabolic disorder. In *Organic Psychiatry*. London: Blackwell, 1978:595-672.
[38] Starkman MN, Zelnik TC, Nesse RM, Cameron OG. Anxiety in patients with pheochromocytomas. *Arch Intern Med* 145:248-252, 1985.
[39] Denko JD, Kaelbling R. The psychiatric aspects of hypoparathyroidism. *Acta Psychiatrica Scandinavica* 38 (suppl. 164):1-70, 1962.
[40] Gorman JM, Fyer AJ, Gliklich J, King D, Klein DF. Mitral valve prolapse and panic disorders. Effect on imipramine. In Klein DF, Rabkin JG, eds.) *Anxiety-New Research and Changing Concepts*, New York: Raven Press, 1981.
[41] Venkatesh A, Pauls DL, Crowe R, et al. Mitral valve prolapse in anxiety neurosis (panic disorder). *Am Heart J* 100:302-305, 1980.
[42] Shear MK, Devereux RB, Kramer-Fox, Mann JJ, Frances A. Panic patients with a low prevalence of mitral valve prolapse in patients with panic disorder. *Am J Psychiatry* 141:302-303, 1984.
[43] Devereux RB, Perloff JK, Reichek N, Josephson ME. Mitral valve prolapse. *Circulation* 54:3-14, 1976.
[44] Mazza DL, Martin D, Spacavento L, Jacobsen J, Gibbs H. Prevalence of anxiety disorders in patients with mitral valve prolapse. *Am J Psychiatry* 143:349-352, 1986.
[45] Liberthson R, Sheehan DV, King ME, Weyman AE. The prevalence of mitral valve prolapse in patients with panic disorders. *Am J Psychiatry* 143:511-515, 1986.
[46] Bowen RC, D'Arcy C, Orchard RC. The prevalence of anxiety disorders among patients with mitral valve prolapse syndrome and chest pain. *Psychosomatics* 32:400-406, 1991.
[47] Rice RL. Symptom patterns of the hyperventilation syndrome. *Am J Med* 8:691-700, 1950.
[48] McKell TE, Sullivan AJ. The hyperventilation syndrome in gastroenterology. *Gastroenterology* 9:6-16, 1947.
[49] Plum F, Posner JB. Diagnosis of stupor and coma (2nd ed.) *Contemporary Neurology Series*. Philadelphia: FA Davis Co., 1972.
[50] Gotoh F, Meyer JS, Takagi Y. Cerebral effects of hyperventilation in man. *Arch Neurol* 12:410, 1965.
[51] Neill WA, Hattenhauer M. Impairment of myocardial O_2 supply due to hyperventilation. *Circulation* 52:854-858, 1975.
[52] Evans DW, Lum LC. Hyperventilation: An important cause of pseudoangina. *Lancet* 1:155-157, 1977.
[53] Christensen B. Studies on hyperventilation II. Electrocardiographic changes in normal man during voluntary hyperventilation. *J Clin Invest* 24:880, 1946.
[54] McHenry PL, Cogan OJ, Elliott WC, Knoebel SB. False-positive ECG response to exercise secondary to hyperventilation. Cineangiographic correlation. *Am Heart J* 79:683-687, 1970.
[55] Parkinson D. Concussion. *Mayo Clin Proc* 52:492-496, 1977.
[56] Leigh D. Psychiatric aspects of head injury. *Psychiatry Digest* 40: 21-32, 1979.
[57] Oppenheimer RD. Microscopic lesions in the brain following head injury. *J Neurology Neurosurgery Psychiatry* 31:299-306, 1968.
[58] Taylor AR, Bell TK. Slowing of cerebral circulation after concussional head injury. A controlled trial. *Lancet* 2:178-180, 1966.
[59] Gronwall D, Wrightson P. Delayed recovery of intellectual function after minor head injury. *Lancet* 2:605-609, 1974.
[60] Sheehan DV. Panic attacks and phobias. *N Engl J Med* 307:156-158, 1982.
[61] Katon W, Roy-Byrne PP. Panic disorder in the medically ill. *J Clin Psychiatry* 50:299-302, 1989.
[62] Sheehan DV, Ballinger J, Jacobsen G. Treatment of endogenous anxiety with phobic hysterical and hypochondriacal symptoms. *Arch Gen Psychiatry*, 37:51-59, 1980.
[63] Katon W. Panic disorder and somatization. Review of 55 cases. *Am J Med* 77:101-106, 1984.
[64] Katon WJ. Chest pain, cardiac disease, and panic disorder. *J Clin Psychiatry* 51(5 suppl):27-30, 1990.
[65] Goldberg R, Morris P, Christian F, Badger J, Chabot S, Edlund M. Panic disorder in cardiac outpatients. *Psychosomatics* 31:168-173, 1990.
[66] Alexander P. Treatment of panic disorder. *RI Medicine* 75:253-257, 1992.
[67] Gordon A. Panic Disorder: A clinical perspective on acute treatment and future research needs. *RI Medicine* 75:262-264, 1992.

Address correspondence to:
Richard J. Goldberg, MD
Rhode Island Hospital
593 Eddy Street
Providence, RI 02902

A critical health problem for your patient. A difficult problem for you to treat.

The Miriam Hospital Weight Management Service offers treatment programs addressing all levels of obesity. With over 10 years' experience in obesity treatment and research, our multidisciplinary team provides the resources needed for safe, medically monitored weight loss and for long-term success in maintaining weight loss.

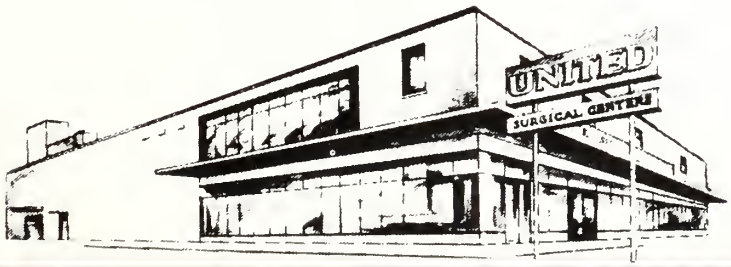
For more information on our programs, or to refer a patient, call:
(401) 861-0870

Portions of our programs may be covered by health insurance.

The Miriam Hospital Weight Management Service
Division of Behavioral Medicine
An affiliate of the Brown University Medical School

There must be a good reason why we've become the trusted back-up resource for more Rhode Island doctors (and their patients) than anyone else.

UNITED SURGICAL CENTERS
The Professionals in Home Health Care Equipment



We carry just about EVERYTHING for Home Health Care . . . which means, everything a patient or convalescent needs to implement the doctor's treatment directions. For Ostomy and Oxygen needs to Orthopedic Appliances, Wheelchairs, Walkers and Hospital Beds, we're here to serve your patients. Our staff is knowledgeable and dedicated to supplying exactly "what the doctor ordered". We've been doing it dependably for many years

That's how we've earned the trust of so many doctors

Medicare and Third Party Claims Accepted and Processed

380 WARWICK AVE., WARWICK
781-2166

Rx C3: Coughs, Colds, Flu...

NDC 0372-0048-16 ONE PINT (473.2 ml.)

S-T FORTE™

SUGAR-FREE© ALCOHOL-FREE

(Revised Formula 1-92)

Each 5ml. contains:

HYDROCODONE BITARTRATE U.S.P. .....2.50 mg.

CHLORPHENIRAMINE MALEATE U.S.P. .....2.0 mg.

CIII

Antitussive Antihistamine

CAUTION: Federal law prohibits dispensing without a prescription.

Does not contain: sugar, alcohol, dyes, saccharin, sorbitol, decongestants, mannitol, or xylitol.

Approved for payment by Medical Assistance.

Oral Rx where permitted by State Law.

1 (800) 638-SCOT or (401) 942-8555

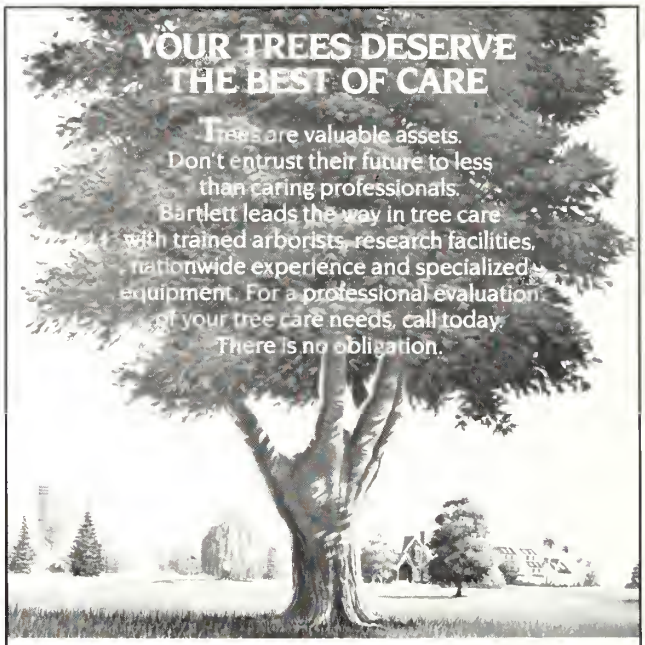
™ Trade Mark since 1956

SCOT-TUSSIN®

PHARMACAL CO., INC.
CRANSTON, RI 02920-0217 (USA)

® T.M. U.S. Patent Office Reg. #657-674

Printed 3/92


YOUR TREES DESERVE THE BEST OF CARE
Trees are valuable assets. Don't entrust their future to less than caring professionals. Bartlett leads the way in tree care with trained arborists, research facilities, nationwide experience and specialized equipment. For a professional evaluation of your tree care needs, call today. There is no obligation.

All Phases of Tree Care: Residential and Commercial

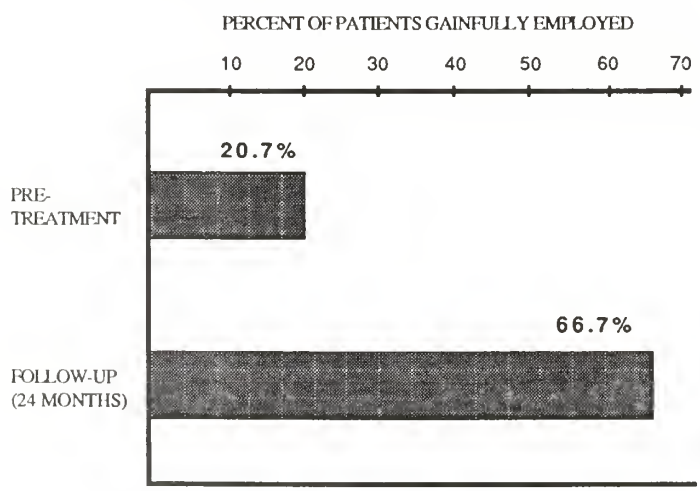
LOCAL OFFICES
Seekonk, MA
508-336-9330
North Kingston, RI
401-884-2885

Scientific tree care since 1907
BARTLETT TREE EXPERTS
Corporate Office STAMFORD, CT

Backed by the Bartlett Research Laboratories and Experimental Grounds
Charlotte North Carolina

1991 Bartlett Tree Experts

"CHRONIC PAIN DOESN'T HAVE TO MEAN CHRONIC DISABILITY FOR YOUR PATIENTS..."



The Chronic Pain Treatment Program
(401) 751-9150

Institute for Behavioral Medicine
120 Wayland Avenue
Providence, Rhode Island 02906-4318

Panic Disorder in Children and Adolescents

Greta Francis, PhD
Douglas R. Robbins, MD
WL Grapentine, MD

Undiagnosed panic disorder may be a significant health problem in children and adolescents. Some of the adolescents and children who have presented for years with school refusal or psychogenic somatic complaints may suffer from this disorder and may benefit significantly from appropriate treatment.

Panic disorder is well-known in adults but has been diagnosed infrequently in children and adolescents. As a result, very little is known about the phenomenon of panic in youngsters. Adults typically report onset of their symptoms in adolescence or earlier, however, and the advent of specific assessment techniques and diagnostic criteria has produced reports of children and adolescents who meet criteria for this diagnosis.[1-5] As with adults, comorbid depressive disorders commonly have been reported in panic-disordered youngsters.[2,3]

Undiagnosed panic disorder may be a significant health problem in children and adolescents. Some of the adolescents and children who have presented for years with school refusal or psychogenic somatic complaints may suffer from this disorder and may benefit significantly from appropriate treatment. Pediatricians see an undetermined number of children with panic disorder, whose most prominent symptoms are somatic.[3] In fact, the label of "hyperventilation syndrome" has been used to describe some of these somatically preoccupied youngsters.[6] The prevalence of panic disorder in children and adolescents is not yet known. The broad overlap of panic symptoms and drug and medical conditions, as outlined in this issue of *Rhode Island Medicine*, adds further confusion.[7] The diagnosis in children and adolescents is made using the same criteria used for adults.[8]

An example of this disorder, which illustrates the spontaneous nature of some of the panic attacks, is the case of a 15-year-old boy who sought a psychiatric evaluation after two late night visits to the local emergency room failed to identify any physical basis for his concern that he was having a heart attack. During the psychiatric evaluation, he indicated that for the past three months he had been preoccupied by intense fear that he would die from a heart attack. Each day he experienced intense attacks of anxiety that came "out of the blue." During the anxiety attacks, he noted the following symptoms: shortness of breath, palpitations, chest pains, nausea, flushes, dizziness, paresthesia, trembling, derealization, and fear that he was about to die. Each attack was followed by persistent worry that he would have another attack. He was unable to identify any situation that seemed to precipitate the attacks; instead, he indicated that they could happen any time.

Avoidant Behaviors

Sometimes youngsters with panic disorder begin to restrict their movements and activities to "prevent" having a panic attack. Commonly avoided situations include driving, crossing bridges, and visiting shopping malls. In these situations, youngsters feel trapped and fearful that they will have a panic attack. They may refuse to attend school or to partici-

Greta Francis, PhD, is Assistant Professor, Department of Psychiatry and Human Behavior, Brown University, Providence, Rhode Island, and Clinical Psychologist and Director of the Anxiety Disorders Clinic, Bradley Hospital, Riverside, Rhode Island.

WL Grapentine, MD, is Assistant Professor, Department of Psychiatry and Human Behavior, Brown University, Providence, Rhode Island, and Associate Medical Director of the Adolescent Practice Team, Bradley, Hospital, Riverside, Rhode Island.

Douglas R. Robbins, MD, is Clinical Associate Professor, Department of Psychiatry and Human Behavior, Brown University, Providence, Rhode Island, and Attending Psychiatrist, Bradley Hospital, Riverside, Rhode Island.

pate in activities outside of the home. Such a pattern of avoidance is consistent with a diagnosis of panic disorder with agoraphobia.

For example, a 16-year-old girl was referred for an inpatient psychiatric evaluation following a year-long history of school avoidance. During a comprehensive diagnostic evaluation, she was diagnosed with panic disorder with agoraphobia. She experienced her first panic attack in a high school auditorium and subsequently began to feel uncomfortable whenever she was in large, enclosed spaces. Initially, she only avoided school on days in which there were assemblies in the auditorium or when she was scheduled for physical education class in the gymnasium. Eventually, she stopped going to school altogether as she became fearful of having a panic attack whenever away from home. She rarely left the house and relied on other family members to accompany her on the infrequent occasions when she ventured outside.

Sometimes youngsters with panic disorders begin to restrict their movements and activities so as to "prevent" having a panic attack.

It is necessary to examine avoidance behavior carefully before assigning a diagnosis of agoraphobia. For example, children may be reluctant to attend school for a variety of reasons, including fear of embarrassment, separation anxiety, depression and noncompliance. For a school-avoidant youngster, panic disorder with agoraphobia should be considered and diagnosed if the child is avoiding school because of fear of having a panic attack.

Diagnostic Overlap in Children and Adolescents

It can be difficult to diagnose panic disorder in youngsters, since panic attacks are experienced by many anxiety-disordered children. For example, a child with separation anxiety disorder may become panicky when separated from his or her parents, or an adolescent with social phobia may become panic-stricken when required to give a speech in front of classmates. In both cases, panic disorder would not be diagnosed because the panic attacks did not occur spontaneously but rather were precipitated by specific anxiety-provoking situations, separation from parent and public speaking, respectively.

Course

Given that the age of onset for panic disorder typically is during adolescence, the panic symptoms of youngsters generally are of recent onset. The relative acuity of the problem can make it difficult to ascertain the clinical significance of the symptoms. A child may need to be observed or evaluated over time to determine whether the panic symptoms are occurring spontaneously or whether such symptoms will persist over time.

The extent to which spontaneous panic symptoms remit if untreated is unclear. Since many youngsters with panic symptoms may seek medical rather than psychiatric evaluations, there may be many cases of panic disorder that never receive psychiatric intervention. Evidence suggests that children treated for hyperventilation syndrome tend to display symptoms into adulthood.[6]

The continuity between juvenile anxiety disorders and adult forms also is not clear. Several studies suggest, however, that many adults with panic disorder have had anxiety symptoms, specifically separation anxiety, since childhood and adolescence.[9,10] Longitudinal studies have not been done to establish clearly the rates of persistence of childhood anxiety disorders or the patterns of evolution and development of anxiety symptoms.[11]

Treatment

The clinical significance of underdiagnosis of panic disorder may be great. While the disorder can cause significant impairment in function in adults – with severe avoidant behavior or depression – it is often highly responsive to treatment.[12,13] The reported child and adolescent cases suggest that the same may be true for cases with juvenile onset.

Given that panic disorder only recently has been studied in children and adolescents, there is virtually no empirical information available as to the treatment of the disorder in youngsters. As such, treaters of panic-disordered youth have looked to the adult literature in which behavioral, cognitive, and pharmacological therapies have been studied and found to be efficacious. Alexander, in this issue, outlines those therapies.[14]

. . . children and adolescents can be taught to do progressive muscle relaxation exercise, identify catastrophizing thoughts, and to participate in graduated exposure.

Barlow and Cerny have developed a comprehensive behavioral treatment manual for panic disorder. Their three component approach includes relaxation training, cognitive restructuring (ie, modifying maladaptive thoughts and teaching coping strategies) and exposure therapy (ie, patient gradually approaches anxiety-provoking situations).[12] While the treatment has been studied primarily with adult patients, it can be modified for treating children and adolescents. For example, children and adolescents can be taught to do progressive muscle relaxation exercises, identify catastrophizing thoughts, and to participate in graduated exposure.

A few studies have reported the treatment of adolescents with panic disorder with agoraphobia. For example, Barlow and Seidner described the use of a multicomponent group therapy package to treat three adolescent patients.[15] Treatment included cognitive restructuring and graduated exposure. Results indicated that two of the three patients significantly improved over the course of treatment and at six-month follow-up.

We have used such cognitive-behavioral strategies in treating children and adolescents with panic disorder. For example, we treated a 14-year-old girl who was diagnosed with panic disorder without agoraphobia. Her initial presenting complaints included excessive anxiety, preoccupation with physical symptoms, and difficulty sleeping. She described feeling very panicky and fearful of dying or losing control when experiencing shortness of breath, palpitations, chest pain, tightness in her throat, sweating, faintness, and trembling. These symptoms were worse at night and when she was in crowded spaces. She did not avoid any situation, although she often felt uncomfortable in the crowded hallways of school. She was fearful of having a panic attack and was unable to distract herself successfully once she became frightened.

A genetic factor in its etiology is suggested by a study of twins in which concordance for panic attacks was five times greater in monozygotic twins than in dizygotic pairs.

This adolescent participated in individual therapy for two months. She monitored her anxiety by keeping a journal of times when she felt nervous, describing what she was doing and thinking at the time. She and her family also were given educational information about anxiety and panic. She was an active and enthusiastic participant in therapy, which included progressive muscle relaxation and cognitive restructuring. She was given an audiotape of the relaxation exercise, which she practiced daily. She also was taught to identify catastrophizing thoughts associated with anxiety, such as "I'm going to feel anxious forever" and "I'm going to die." Self-monitoring allowed her to see a relationship between her thoughts and feelings, and she noticed that her catastrophizing thoughts made her anxiety level increase. Once she started to identify these thoughts, she began to catch her anxiety early on, before it reached panic proportions. When she noticed herself feeling a little bit nervous, she practiced using coping statements such as "It is okay to feel a little nervous" and "My anxiety level will come down." By the end of treatment, her sleep had improved, and she no longer experienced panic attacks.

Successful pharmacologic treatment has been known since early explorations of the effects of tricyclic antidepressants, especially imipramine.[13] Imipramine usually blocks the occurrence of the panic attacks but does not reduce directly the anticipatory anxiety or phobic avoidance and dependency that are often quite incapacitating. The concurrent use of behavioral treatment, such as systematic desensitization to situations associated with panic attacks, is often needed. The effect on panic is independent of whether or not patients have associated depression.

Interest in pharmacological treatment also reflects suggestive evidence of a pathophysiological basis to this disorder. A genetic factor in its etiology is suggested by a study of twins, in which concordance of panic attacks was five times greater in monozygotic twins than in dizygotic pairs.[17] A specific physiological factor is suggested by the well replicated finding that an intravenous infusion of sodium lactate induces panic attacks in individuals with panic disorder but not in normal subjects or psychiatric controls; and that medications which are useful clinically, eg, tricyclic antidepressants, can block this effect.[18]

Controlled studies of drug treatment in children and adolescents have not yet been reported, but many of the case reports include descriptions of striking pharmacologic effects of tricyclic antidepressants.[3] Fluoxetine and monoamine oxidase inhibitors have also shown efficacy in adults,[12,14,15] but they have not yet been studied in children and adolescents.

The following case illustrates the role of despiramine, a tricyclic antidepressant, in the treatment of an adolescent with panic disorder. A 16-year-old boy was hospitalized because of persistent rumination about killing himself. A diagnosis of major depression was made, and his poor school attendance was thought to be due to depression. He described episodes of anxiety, however, with very abrupt onset associated with dypsnea, pallor, sweating, and faintness that occurred two to five times per week. Many of these attacks occurred in crowded situations, notably in the halls of his high school or in a shopping mall, and he had begun to avoid such places, living an increasingly restricted and reclusive life. Other panic attacks did not have obvious precipitants. Pressure to attend school and the frustration of his family appeared to play a role in the development of his depressive symptoms, which were of more recent onset. Attempts to help him monitor his anxiety by anticipating and verbalizing his response to provocative situations and gradually increasing his exposure to school and busy stores met with obstinate resistance, which worsened severely following each new attack. On despiramine, 150 mg at bedtime, no further panic attacks occurred, and gradually, he began to respond to the behavioral and supportive treatment, returning home and to high school.

. . . clinicians should be aware of the possibility that panic disorder is the reason some children and adolescents refuse to go to school or to leave home, or present with somatic complaints or depression.

In the absence of controlled studies clarifying treatment strategies, a pragmatic approach to a child or adolescent with panic disorder is to begin with a trial of behaviorally oriented individual and family psychotherapy. Many patients will respond to this, without medication. If panic attacks continue, a trial of medication, eg, despiramine or imipramine, is indicated, in conjunction with continuing therapy.

Conclusion

We can hope to have better data on the prevalence of panic disorder and its treatment soon. At this time, clinicians should be aware of the possibility that panic disorder is the reason some children and adolescents refuse to go to school or to leave home, or present with somatic complaints or depression. In such cases, specific behavioral and pharmacological treatment may be very effective.

References

1. Alessi NE, Magen J. Panic disorder in psychiatrically hospitalized children. *Am J Psychiatry* 145:1450-1452, 1988.
2. Alessi NE, Robbins DR, Dilsaven SC. Panic and depressive disorders among psychiatrically hospitalized adolescents. *Psychiatry Research* 20:275-283, 1987.
3. Black B, Robbins DR. Panic disorder in children and adolescents. *J Am Acad Child Adol Psychiatry* 29:36-44, 1990.
4. Last CG, Strauss CC. Panic disorder in children and adolescents *J Anxiety Disorders* 3:87-95, 1989.
5. Moreau DL, Weissman MM, Warner V. Panic disorder in children at high risk for depression. *Am J Psychiatry* 146:1059-1060, 1989.
6. Herman S, Stickler G, Lucas A. Hyperventilation syndrome in children and adolescents: Long-term follow-up. *Pediatrics* 67:183-187, 1981.
7. Goldberg, R. Medical aspects of panic disorder. *RI Medicine* 75:265-270, 1992.
8. White K. Anxiety disorders: An overview. *RI Medicine* 75:241-244, 1992.
9. Klein DF. Delineation of two drug responsive anxiety syndromes. *Psychopharmacologia* 5:397-408, 1964.
10. Gittelman R, Last CG. *Anxiety Disorder in Children*. Newbury Park: Sage Publications, Inc., 1989.
11. Gittelman R. *Anxiety Disorders of Childhood*. New York: The Guilford Press, 1986.
12. Barlow DH, Cerny JA. *Psychological Treatment of Panic*. New York: The Guilford Press, 1988.
13. Klein DF, Gittelman R, Quitkin F, Rifkin A. *Diagnosis and Drug Treatment of Psychiatric Disorders: Adults and Children* (2nd Ed). Baltimore: Williams and Wilkins, 1980.
14. Alexander P. Treatment of panic disorder. *RI Medicine* 75:253-257, 1992.
15. Barlow DH, Seidner AL. Treatment of adolescent agoraphobia: Effects on parent-adolescent relations. *Beh Res Ther* 21:519-526, 1983.
16. Solyom L, Solyom C, Ledwidge B. Fluoxetine in panic disorder. *Can J Psychiatry* 36:378-380, 1991.
17. Tongersen S. Genetic factor in anxiety disorders. *Arch Gen Psychiatry* 40:1085-1089, 1983.
18. Kelly D, Mitchell-Heggs N, Sherman D. Anxiety in the effects of sodium lactate assessed clinically and physiologically. *Br J Psychiatry* 119:468-470, 1971.

Address correspondence to:
Greta Francis, PhD
Bradley Hospital
1011 Veterans Memorial Parkway
Riverside, RI 02915

YOUR SPECIALTY IS WORTH AN EXTRA $8,000 A YEAR.

If you're a resident in any of the following specialties:

- anesthesiology
- cardiac/thoracic surgery
- orthopedic surgery
- pediatric surgery
- general surgery
- peripheral/vascular surgery
- neurosurgery
- colon/rectal surgery
- plastic surgery

you could be eligible for an $8,000 annual stipend in the Army Reserve's Specialized Training Assistance Program.

You'll also be using your skills in a variety of challenging settings, from major medical centers to field hospitals, and there are opportunities for conferences and continuing education.

We know your time is valuable, so we'll be flexible about the time you serve. Your immediate commitment could be as little as two weeks a year, with a small added obligation later on. If you'd like to talk to an Army Reserve physician, or if you'd like more information about the stipend program or other medical opportunities, call our experienced Army Reserve Medical Counselor:

Call Collect (203) 624-5325
Cpt. John Grimes
U.S. Army Reserve Medical Dept.
414 Chapel St., New Haven, CT 06511

BE ALL YOU CAN BE.®
ARMY RESERVE

Comorbidity of Panic Disorder and Substance Use Disorders

Timothy I. Mueller, MD
Robert M. Swift, MD, PhD

Some individuals with anxiety disorders use drugs and/or alcohol to excess, presumably to help cope with their situation.

Anxiety is a universal human experience. Yet, for some individuals anxiety occurs in situations not usually considered anxiety-provoking, and the intensity of anxiety becomes debilitating. These individuals are considered to have an anxiety disorder. Several types of anxiety disorders are described in the Revised Third Edition of the *Diagnostic and Statistical Manual* of the American Psychiatric Association (*DSM-III-R*) and are discussed by White in this issue of *Rhode Island Medicine*, with the focus on panic disorder.[1] The experience of such intense anxiety is so unpleasant that persons afflicted with these disorders avoid situations that trigger anxiety. Some individuals with anxiety disorders use drugs and/or alcohol to excess, presumably to help cope with their situation.

Timothy I. Mueller, MD, is Research Associate, Department of Psychiatry and Human Behavior, Brown University, Providence, Rhode Island.

Robert M. Swift, MD, PhD, is Assistant Professor, Department of Psychiatry and Human Behavior, Brown University, Providence, Rhode Island, and Director of Psychiatry, Roger Williams Medical Center, Providence, Rhode Island.

Strictly speaking, comorbidity signifies the co-occurrence of any two diagnoses. In psychiatry, one generally speaks of the co-occurrence of a major psychiatric disorder such as schizophrenia or major depression and any other major psychiatric disorder also coded on Axis I of the *DSM-III-R* multi-axial diagnostic system. "Dual diagnosis" is a popular designation also used to indicate this co-occurrence. In the anxiety disorders and in panic disorder in particular, the occurrences of depression and substance use disorders have a special position, since they co-mingle at a rate that exceeds their association by chance. This report will discuss the comorbid mixture of panic disorder and substance use disorders with special attention on alcoholism.

Population surveys typically have focused on patients who seek treatment for either a psychiatric disorder or a substance use disorder. Studies of psychiatric patients with substance-use disorders and studies of substance-abusing patients with mental health disorders have shown rates of comorbidity in the range of 20% to 70%, depending on the stringency of diagnostic criteria.[2-4]

The field's understanding of the scope of this issue has been immeasurably aided by the data provided by the National Institute of Mental Health Epidemiologic Catchment Area Program (ECA) survey that estimated the rates of psychiatric disorders in the US population through its structured interviews of 20,291 people in five areas of the United States. A recent report by Regier et al,[5] details the comorbidity of mental disorders with substance use disorders. Table 1 summarizes the findings for some representative mental disorders, with attention to panic and the anxiety disorders. Substance use disorders are found to occur in about 36% of patients with panic disorder. The similarity between the symptoms of panic disorder and drug intoxication or withdrawal suggests an etiologic relationship.[6] Panic symptoms are observed frequently in intoxication with cocaine and stimulants, and withdrawal from alcohol and sedatives can mimic the symp-

ABBREVIATIONS USED:

DSM: Diagnostic and Statistical Manual
ECA: Epidemiologic Catchment Area program
MAOIs: Monoamine oxidase inhibitors

toms of panic disorder.[7] In addition, the sedative and anxiolytic properties of many of the drugs of abuse may lead to their self-administration in patients with panic disorder. The self-medication hypothesis holds that psychoactive substances are preferentially used by people to treat their dysphoric states.[8] It is the success of this therapeutic match and the addictive nature of many psychoactive substances that theoretically leads to comorbid abuse and dependence.

An important distinction in this field relies on the idea of a primary versus secondary disorder. By this method of categorization, the temporal relation of one disorder to the other determines its designation as primary or secondary. Thus, if an individual's alcoholism began at age 16, and their panic disorder began at age 21, they could be called a primary alcoholic or a secondary panic patient. Conversely, a primary panic patient with comorbid alcoholism would have had the onset of his or her alcoholism preceded by the onset of the panic disorder. By this logic, the order of onset offers a suggestive causal relationship. If only primary panic is seen in patients with comorbid alcoholism, it would suggest that alcohol is used to treat panic symptoms. Alternatively, alcohol would appear to be the cause of panic disorder if only secondary panic is seen.

There are empirical data to suggest that important temporal relations exist for specific substance use and anxiety disorder comorbidities. A recent review on the comorbidity of alcohol abuse and anxiety disorders notes that uncomplicated panic disorder has no consistent relationship to the onset of alcohol abuse, whereas panic with agoraphobia usually precedes the onset of alcoholism.[9] This temporal relationship would suggest that alcohol abuse may not have a causal relationship to uncomplicated panic, whereas patients with panic and agoraphobia may use alcohol to self-medicate. By this line of reasoning, untreated panic with agoraphobia can lead to alcohol abuse or dependence in susceptible people.

Table 1. **Lifetime Prevalence Rates for Substance Use Disorder Co-morbidity with Selected Mental Health Disorders‡**

	Lifetime Prevalence	Lifetime Prevalence With Comorbid SUD*	Odds Ratio**
Any SUD*	16.7%	–	–
No mental disorder	77.5%	13.2%	1.0
Any mental health disorder other than SUD*	22.5%	28.9%	2.7
Schizophrenia	1.4%	47.0%	4.6
Major depression	5.9%	27.2%	1.9
Any anxiety disorder	14.6%	23.7%	1.7
Panic disorder	1.6%	35.8%	2.9

*Substance Use Disorder

**Odds Ratios are calculated for co-morbid risk compared to a non-affected population, ie, a population without the diagnosis in the row.

‡ Adapted from Regier et al, *JAMA* 1990; 264:2511-2518.

The self-medication hypothesis holds that psychoactive substances are preferentially used by people to treat their dysphoric states.

In this same report, a summary of the family studies in this area also suggests specificity in the association between panic and alcoholism. Compared to normal controls, there is only a slightly greater than average risk of alcoholism in the relatives of family members with uncomplicated panic, compared to a three times risk for alcoholism in relatives of family members with panic and agoraphobia. Through such analyses, the field may come closer to understanding the specific nature of the comorbidity of panic disorder and alcoholism, and possibly unravel common etiologic or causal associations.

Outcome

The data for outcomes in patients with comorbid disorders is tied less specifically to psychiatric diagnoses. It is generally held that it is the degree of psychopathology rather than the specific diagnosis that foretells a more unfavorable outcome for these patients.[10,11] An important exception to this general rule is the report by Weissman *et al*, which shows an increased risk of suicide in patients with panic disorder and alcohol or drug abuse.[12] This report, using the ECA data, convincingly corroborated earlier evidence and demonstrate increased suicide attempts in subjects with panic disorder compared to subjects with any other psychiatric diagnosis and no psychiatric diagnosis, with odds ratios of 2.62 and 12.18 respectively. This risk was increased even further if panic patients were comorbid for alcohol abuse (odds ratio of 3.28) or drug abuse (odds ratio of 4.03), compared to panic patients without comorbidity.

Case Example

A 42-year-old white male with a long history of alcohol dependence, characterized by multiple hospitalizations for alcohol detoxification and withdrawal, also has panic disorder with agoraphobia. The patient attributes his alcohol use to his need to control his panic and says he is unable to attend Alcoholics Anonymous meetings due to agoraphobia. Despite his history of alcohol use, he does not have medical complications from his illness.

He has been treated with clorazepate (Tranxene) for his panic symptoms

with some relief but with little change in the tempo of his alcohol use. During one of his hospitalizations for alcohol detoxification, his clinicians strongly felt that he should not take clorazepate due to the potential for abuse and his "addictive nature." He was, therefore, detoxified from the clorazepate, and as an outpatient, placed on a variety of medication trials in an attempt to control the panic disorder.

Compared to normal controls, there is only a slightly greater than average risk of alcoholism in the relatives of family members with uncomplicated panic, compared to a three times risk for alcoholism in relatives of family members with panic and agoraphobia.

Fluoxetine (Prozac), despiramine, nortriptyline, bupropion (Wellbutrin), buspirone (BuSpar), and tranyclypromine (Parnate) were all tried in turn with no significant remission in his panic. The patient was then placed on clonazepam (Klonopin), 1 mg twice a day with good results. He continues to use alcohol. His involvement in alcohol treatment is sporadic. What is the clinician to do? There are no easy answers to his question, and success is often elusive. This case example illustrates the clinician's dilemma and the need for more research to guide our hands in this difficult area.

Treatment

The treatment of panic crystallizes the dilemma of using psychopharmacologic agents in the substance-abusing population. The benzodiazepines are the most effective medications for treating the acute symptoms of panic. Though the evidence is not universal, the addictive potential of these medications may be increased in people with substance abuse. Fortunately, there are alternative treatments available as outlined in the accompanying articles by Alexander and Gordon in this issue of *Rhode Island Medicine*.[13,14] The behavioral therapies, especially if they occur in a group format, may be especially useful for substance abusers, who can apply their new learning to help control another unwanted behavior, ie, substance abuse. Tricyclic antidepressants are effective in panic. Unfortunately, they present some special risk in substance abusing patients with a history of seizures, since they lower the seizure threshold. Though the monoamine oxidase inhibitors (MAOIs) also are effective in treating panic, the potential adverse reaction with red wine, many spirits and stimulant drugs makes their use problematic for this population.

The information about the temporal relationship between alcohol use and specific anxiety disorders may be helpful in guiding treatment for specific categories of patients. For example, patients with uncomplicated panic, which appears to have no typical relation to alcohol abuse, may be better treated by focusing on the alcohol abuse, using non-pharmacologic therapies for panic disorder and avoiding the complications of using potentially addicting benzodiazepines. Conversely, if alcohol is used to treat agoraphobic symptoms in patients with panic and agoraphobia, the clinician may be in a better position to judiciously prescribe potentially addicting medication, ever mindful of the patient's demonstrated ability to develop dependence. The issues often can become more complex in the interface with the treatment community, which often has a strong negative position about the use of potentially abusable or addictive medications.

The treating physician is often left with the unhappy situation of using the benzodiazepines for this group of people, as was the case in the clinical example we presented. Several general cautions are in order. Treatment of the panic disorder must proceed on a background of active treatment of the substance use disorder, involving the prerequisite addiction specialists and self-help resources. Alcohol and drug sobriety must be a condition of continued drug prescription. The patient must not be getting benzodiazepines from another source. In general, long-acting benzodiazepines with slow onset of action, ie, clonazepam (Klonopin), are preferable to short acting, rapid onset agents, ie, lorazepam (Ativan) or alprazolam (Xanax). The difficulty is that the slow onset agents are much better for preventing an attack than treating the acute symptoms. Prescriptions must be controlled strictly by the physician, and both the patient and the physician must be willing to confront "uncomfortable" feelings about how the treatment is progressing. This especially allows the physician to address the issues of escalating doses, "losing" medications, and asking for premature refills.

The treatment of panic crystallizes the dilemma of using psychopharmacologic agents in the substance abusing population.

Fortunately, there is suggestive evidence that the risk for addictive prescription of these agents may be overstated.[15] In our experience, many such patients can be treated successfully and eventually tapered off of their benzodiazepines, while maintaining their sobriety from other drugs.

Conclusions

There is a greater than average likelihood that patients with panic disorder will have a co-existing substance abuse disorder. The ECA demonstrates that 36% of people with panic disorder have a lifetime diagnosis of an alcohol or drug use disorder. There may be some specificity in the temporal association of alcohol use and panic disorder with agoraphobia, lending important evidence for a causal relationship between the two disorders. Though treatment presents challenging issues in this group, a flexible combination of psychotherapeutic/behavioral and judicious pharmacologic therapies can be successful and rewarding in most patients.

References

1. White K. Anxiety disorders: An overview. *RI Medicine* 75:241-244, 1992.
2. Kranzler HR, Liebowitz NR. Anxiety and depression in substance abuse. *Med Clin North Amer* 72:867-885, 1988.
3. Ross HE, Glaser FB, Germanson T. The prevalence of psychiatric disorders in patients with alcohol and other drug problems. *Arch Gen Psychiatry* 45:1023-1031 1988.
4. Schuckit MA, Monteiro MG. Alcoholism, anxiety and depression. *Br J Addiction* 83:1373-1380, 1988.
5. Reiger DA, Farmer ME, Rae DS, *et al.* Comorbidity of mental disorders with alcohol and other drug abuse. *JAMA* 264:2511-2518, 1990.
6. George DT, Zerby A, Noble S, Nutt DJ. Panic attacks and alcohol withdrawal: Can subjects differentiate the symptoms? *Biol Psychiatry* 24:240-243, 1988.
7. Goldberg R. Medical aspects of panic disorder. *RI Medicine* 75:265-270, 1992.
8. Khantzian EJ. The self-medication hypothesis of addictive disorders: Focus on heroin and cocaine dependence. *Am J Psychiatry* 142:1259-1264, 1985.
9. Kushner MG, Sher KJ, Beitman BD. The relation between alcohol problems and the anxiety disorders. *Am J Psychiatry* 147:685-695, 1990.
10. Rounsaville BJ, Dolinsky ZS, Babor TF, Meyer RE. Psychopathology as a predictor of treatment outcome in alcoholics. *Arch Gen Psychiatry* 44:505-513, 1987.
11. Stoffelmayer BE, Benishek LA, Humphreys K, *et al.* Substance abuse prognosis with an additional psychiatric diagnosis: Understanding the relationship. *J Psychoactive Drugs* 21:145-152, 1989.
12. Weissman, MM, Klerman GL, Markowitz JS, Ouellette R. Suicidal ideation and suicide attempts in panic disorder and attacks. *N Eng J Medicine* 321:1209-1214, 1989.
13. Alexander P, Treatment of panic disorder. *RI Medicine* 75:253-257, 1992.
14. Gordon A. Panic Disorder: A clinical perspective on acute treatment and future research needs. *RI Medicine* 75:262-264, 1992.
15. Ciraulo DA, Sands BF, Shader RI. Critical review of liability for benzodiazepine abuse among alcoholics. *Am J Psychiatry* 145:1501-1506, 1988.

Address correspondence to:
Timothy I. Mueller, MD
Psychiatry Research
Butler Hospital, Duncan Building
345 Blackstone Boulevard

June, 1992

Contents

RHODE ISLAND
MEDICINE

Clinical Observations in Rhode Island

NURSE ANESTHESIA SERVICES OF NEW ENGLAND (NASNE)

serving Rhode Island hospitals with local CRNAs

- Specialists in TEMPORARY and PERMANENT placement of CRNAs
- NASNE provides local, experienced, highly-qualified CRNAs to Rhode Island hospitals
- NASNE's use of local CRNAs reduces your staffing costs by avoiding travel and other associated expenses
- Dependable and personalized service is provided by a staff that understands you and your scheduling needs

NASNE – the Rhode Island Specialists
Call us at 1-800-531-5319

YOCON®
YOHIMBINE HCl

Description: Yohimbine is a 3a-15a-20B-17a-hydroxy Yohimbine-16a-carboxylic acid methyl ester. The alkaloid is found in Rubaceae and related trees. Also in Rauwolfia Serpentina (L) Benth. Yohimbine is an indolalkylamine alkaloid with chemical similarity to reserpine. It is a crystalline powder, odorless. Each compressed tablet contains (1/12 gr.) 5.4 mg of Yohimbine Hydrochloride.

Action: Yohimbine blocks presynaptic alpha-2 adrenergic receptors Its action on peripheral blood vessels resembles that of reserpine, though it is weaker and of short duration. Yohimbine's peripheral autonomic nervous system effect is to increase parasympathetic (cholinergic) and decrease sympathetic (adrenergic) activity. It is to be noted that in male sexual performance, erection is linked to cholinergic activity and to alpha-2 adrenergic blockade which may theoretically result in increased penile inflow, decreased penile outflow or both.

Yohimbine exerts a stimulating action on the mood and may increase anxiety. Such actions have not been adequately studied or related to dosage although they appear to require high doses of the drug. Yohimbine has a mild anti-diuretic action, probably via stimulation of hypothalmic centers and release of posterior pituitary hormone.

Reportedly, Yohimbine exerts no significant influence on cardiac stimulation and other effects mediated by B-adrenergic receptors, its effect on blood pressure, if any, would be to lower it; however no adequate studies are at hand to quantitate this effect in terms of Yohimbine dosage.

Indications: Yocon® is indicated as a sympathicolytic and mydriatric. It may have activity as an aphrodisiac.

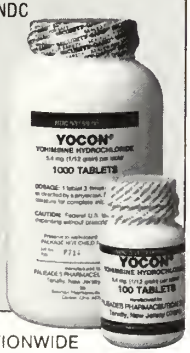
Contraindications: Renal diseases, and patient's sensitive to the drug. In view of the limited and inadequate information at hand, no precise tabulation can be offered of additional contraindications.

Warning: Generally, this drug is not proposed for use in females and certainly must not be used during pregnancy. Neither is this drug proposed for use in pediatric, geriatric or cardio-renal patients with gastric or duodenal ulcer history Nor should it be used in conjunction with mood-modifying drugs such as antidepressants, or in psychiatric patients in general.

Adverse Reactions: Yohimbine readily penetrates the (CNS) and produces a complex pattern of responses in lower doses than required to produce peripheral a-adrenergic blockade. These include, anti-diuresis, a general picture of central excitation including elevation of blood pressure and heart rate, increased motor activity, irritability and tremor. Sweating, nausea and vomiting are common after parenteral administration of the drug.[1,2] Also dizziness, headache, skin flushing reported when used orally.[1,3]

Dosage and Administration: Experimental dosage reported in treatment of erectile impotence.[1,3,4] 1 tablet (5.4 mg) 3 times a day, to adult males taken orally. Occasional side effects reported with this dosage are nausea, dizziness or nervousness. In the event of side effects dosage to be reduced to ½ tablet 3 times a day, followed by gradual increases to 1 tablet 3 times a day. Reported therapy not more than 10 weeks.[3]

How Supplied: Oral tablets of Yocon® 1/12 gr. 5.4 mg in bottles of 100's NDC 53159-001-01 and 1000's NDC 53159-001-10.



References:

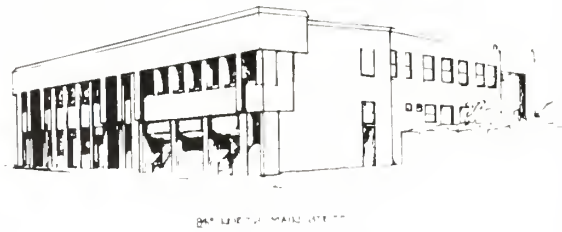
1. A. Morales et al., New England Journal of Medicine: 1221. November 12, 1981.
2. Goodman, Gilman — The Pharmacological basis of Therapeutics 6th ed., p. 176-188. McMillan December Rev. 1/85.
3. Weekly Urological Clinical letter, 27:2, July 4, 1983.
4. A. Morales et al., The Journal of Urology 128: 45-47, 1982.

Rev. 1/85

AVAILABLE AT PHARMACIES NATIONWIDE

PALISADES PHARMACEUTICALS, INC.
219 County Road
Tenafly, New Jersey 07670
(201) 569-8502
1-800-237-9083

CONDOMINIUMS
FOR SALE OR LEASE



845 NORTH MAIN STREET
PROVIDENCE, RI

- Professional Office and Retail Space
- Convenient Access to I-95
- Minutes from downtown Providence, the Hospitals and Universities
- Ample On-Site Parking

CONTACT: CINDY MORSE, CCIM
PETER M. SCOTTI & ASSOCIATES
CCIM
60 Ship Street, Providence, RI 02903
401-421-8888

Need Information about Businesses? Call the Business *INFOLINE!*

There are over 9 million businesses in the U.S. – and finding information about them can be virtually impossible, especially when you need it *fast*. But now there's a way . . . a revolutionary new service called *Business INFOLINE!* Need to know the address and phone number for "XYZ Company" somewhere in Florida, or the name and phone number of a "Cadillac Dealer" in Palm Beach? Even telephone company directory assistance can't help you in these situations . . . but we can!

For example . . .

"Your BMW breaks down on the interstate, and you need to know if there 's a dealer in the next town."

"An out-of-town company is trying to sell you vinyl siding for your house and you need more information about them – how long the company has been in business, and how many employees they have."

"You're planning a vacation in the Pacific Northwest, and you want to line up things for the kids to do. So you need to find the amusement parks and zoos in Oregon and Washington."

"A friend gave you a tip that "Apex Industries" would be a good investment, but you want to know more. What do they do? What are their approximate annual sales?"

The Business INFOLINE is indispensable for home or office? And the cost is *only* $3.00 for the first minute and $1.50 for each additional minute, conveniently billed to your phone number. The service is available Monday through Friday, 7:00 a.m. to 6:00 p.m., Central Time.

Dial 1-900-896-0000

Ask for Ext. #195

Money-back Guarantee if not satisfied.

A Service of American Business Information • 5711 So. 86th Circle • Omaha, NE 68127

HEALTH BY NUMBERS

Rhode Island
Department of Health
Barbara A. DeBuono, MD, MPH
Director of Health

Workplace Smoking Policies of Rhode Island Employers

Exposure to environmental tobacco smoke (ETS) in the workplace is of growing concern to both employees and public health officials. The Rhode Island Workplace Smoking Pollution Control Act of 1986 requires all private Rhode Island businesses to maintain, ie, implement and enforce, a workplace smoking policy for their employees. Recently, the Rhode Island Department of Health, Office of Environmental Health Risk Assessment, conducted a telephone survey of Rhode Island businesses to obtain data on existing workplace smoking policies.

Ninety-three businesses were selected randomly from publications produced by the Rhode Island Department of Economic Development,[1] and they were contacted by telephone using a standard survey protocol. The most knowledgeable respondent at each business was asked whether the business had a smoking policy, and if so, was asked to briefly describe the policy. When written policies were available, the questioner requested them and compared information obtained in the telephone interview with written policies. Discrepancies between the two were found to be minimal and were resolved in favor of written policies.

Smoking policies were categorized in the following manner: "smoke-free" (no smoking allowed anywhere on indoor company property), "restrictive" (smoking allowed only in a section of the workplace cafeteria, in private offices with the door shut, or in designated lounges or rooms), "less restrictive" (smoking allowed in areas permitted by a "restrictive" policy, and in any of the following areas: corridors, conference rooms, rest rooms, and /or stairwells), "least restrictive" (smoking not restricted beyond the extent to which there is a conflict between nonsmoker and smoker where management must become involved in the dispute), and "no policy" (smoking issues are not addressed either officially or unofficially by management).

Of the 93 facilities contacted, 26% had "smoke-free" policies, 37% were "restrictive," 15% were "less restrictive," 13% were "least restrictive," and 10% had "no policy" (Figure 1).

In comparison to national rates, . . . Rhode Island businesses reported a similar rate of smoking policies.

Analysis of the results by business category indicated that manufacturing facilities generally had less restrictive policies than non-manufacturers. Only 12% of the manufacturing firms surveyed reported "smoke-free" policies, as compared to 33% of non-manufacturing firms. The data for the remaining policies were similar for manufacturing and non-manufacturing firms, except that manufacturing firms were more likely to have no policy (15% vs 6% respectively) (Figure 2).

Business size was also observed to impact policy types. "Smoke-free" policies were most common in businesses with fewer than 49 employees (49%), as compared to 24% for firms with 50 to 99 employees and 18% for firms with 100 or more employees (Figure 3).

In comparison to national rates, the surveyed Rhode Island businesses reported a similar rate of smoking policies in place compared to the rest of the country. A 1991 Bureau of National Affairs (BNA) survey reports an 85% policy rate for the nation, while the Rhode Island businesses reported a rate of 89%. However, only 26% of the Rhode Island firms contacted in the study reported having completely "smoke-free" workplaces, while the national rate according to the BNA is 34% (Figure 4).

References

1. Rhode Island Directory of Manufacturers. Rhode Island Department of Economic Development, January 1991. Companies Employing 50 to 200 Employees. Rhode Island Department of Economic Development, November 1991. Rhode Island Business Firms with 100 or More Employees. Rhode Island Department of Economic Development, February 1991.
2. "SHRM-BNA Survey No. 55, Smoking in the Workplace: 1991," Bulletin to Management, BNA Policy and Practice Series. Bureau of National Affairs, Inc., Washington DC, August 1991.

Submitted by the Office of Environmental Health Risk Assessment, Rhode Island Department of Health; Dana K. Hanson, Intern; Robert R. Vanderslice, PhD, Toxicologist, Bela T. Matyas, MD, MPH, Chief. Health by Numbers *is edited by Jay S. Buechner, PhD, and William J. Waters, Jr, PhD.*

Figure 1. **Smoking Policies of Rhode Island Employers (93 facilities contacted)**

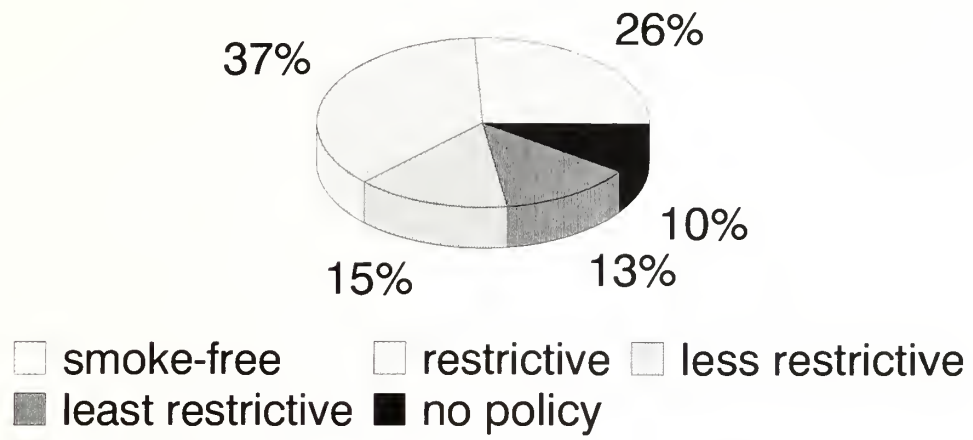


Figure 2.**Smoking Policy Breakdown by Business Category (total of 93 facilities contacted)**

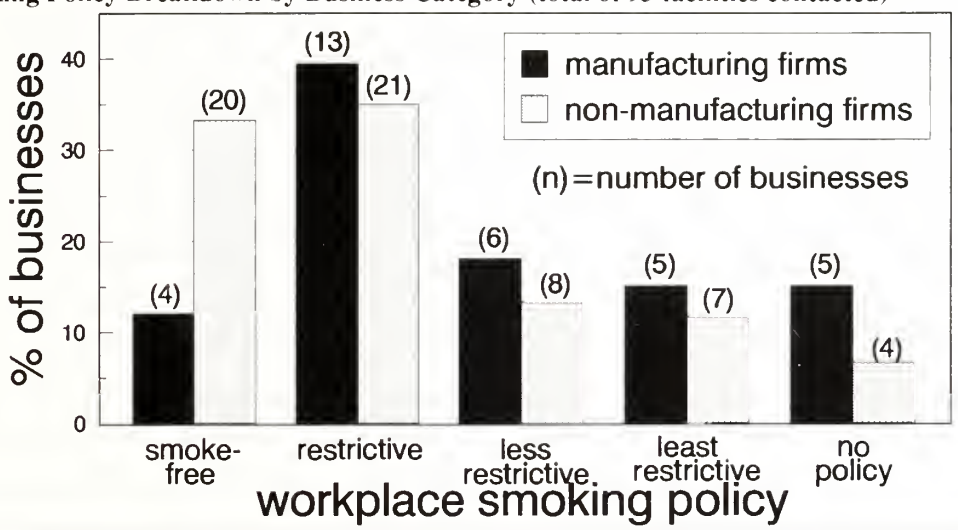


Figure 3. **Policy Breakdowns by Business Size (total of 93 facilities contacted)**

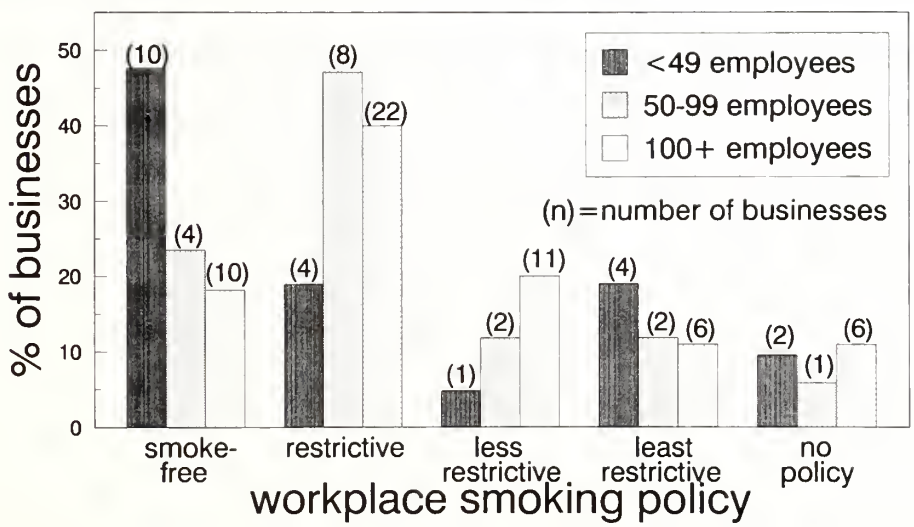
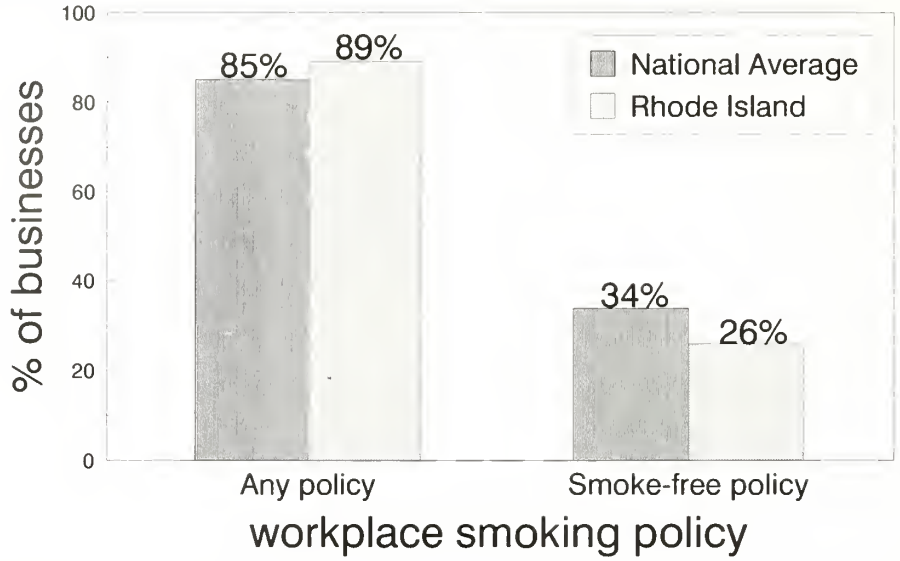


Figure 4. **National Comparison of Smoking Policies (data from the Bureau of National Affairs)**



RUN A SPECIAL PRACTICE.

Today's Air Force has special opportunities for qualified physicians and physician specialists. To pursue medical excellence without the overhead of a private practice, talk to an Air Force medical program manager about the quality lifestyle, quality benefits and 30 days of vacation with pay each year that are part of a medical career with the Air Force. Discover how special an Air Force practice can be. Call

USAF Health Professions
TOLL-FREE
1-800-423-USAF

AIR FORCE

THE RHODE ISLAND MEDICAL JOURNAL

The Official Organ of the Rhode Island Medical Society
Issued Monthly under the direction of the Publication Committee

VOLUME I
NUMBER I

PROVIDENCE, R. I., JANUARY, 1917

PER YEAR $2.00
SINGLE COPY, 25 CENTS

THE RHODE ISLAND MEDICAL JOURNAL HERITAGE

Ninety Years Ago
(May, 1902)

Frank E. Burdick, MD, a practicing physician of Providence offers a case report of a 12-year-old male who died of sunburn. The child was described as "brunette, of delicate constitution, with tendency to pulmonary disease." He celebrated his twelfth birthday by a trip to a bathing beach on the west shore of the bay. After a swim, he played on the beach for three to four hours, without protective clothing, and was exposed to the direct rays of the sun. Four days later he was brought to the attention of the author because of painful burns on his back. The back was described as diffusely reddened, with numerous vesicles, some appearing pustular. Some exfoliation of the back was also present. Temperature and pulse were slightly elevated. Three days later there were numerous small sloughs. On the ninth day the child complained of epigastric pain (with tenderness), fever and vomiting. Stools, the next day, were tarry and later mixed with frank blood. High fever and delirium then appeared and the child died 12 days after the extensive exposure to the sun. No post mortem examination was permitted. The author quotes Curling's insightful studies of duodenal ulceration in cases of burns and concludes that, "the death was due to lesions of the intestinal tract as a secondary result of the sunburn."

Herbert Terry, MD of Providence reports on a case of puerperal eclampsia in a primipara eight months pregnant. The patient was hospitalized because of convulsions. A healthy baby was delivered, but the patient continued to convulse, developed a high fever and became unconscious. After vigorous antipyretic treatment, including immersion baths, she slowly recovered but showed a transitory hemiplegia during her convalescence. Additional treatment included subcutaneous saline injections, croton oil, pilocarpine, chloral hydrate and bromides by rectum, cream of tartar water and lactate of strontium.

The minutes of the Providence Medical Association are printed in this issue. Dr C Higgins describes his experience with 75 cases of cancer of the cervix. Dr J McKenna presented a paper on the treatment of pneumonia with anti-pneumococcic serum. The following resolution was adopted; "it was voted: that the movement by the City Council to license milkmen and dealers in milk, with proper sanitary regulations, meets with the hearty approval of this Association."

The lead editorial discusses heredity and tuberculosis. Mention is made of a recent study of 242 cases which indicates that instead of a predisposition, the child of tuberculous parents inherits a relative immunity – which is contrary to prevailing views that there is a hereditary disposition to consumption. The editorial concludes: Too much reliance should not be placed in the figures of statistics but at present the evidence is greatly in favor of the belief that actual inheritance of the disease is of the rarest occurrence and that the so-called inherited predisposition is of comparatively minor importance.

The second editorial entitled "A Dangerous Precedent" expresses profound concerns over a rumor alleging that St Joseph's Hospital of Providence will accept patients who had previously been cared for by the New Haven Railroad. The editorial states: "To our mind this establishes a dangerous precedent and places the hospital in a mercenary light which ill befits a charitable institution. If a hospital is a charitable institution, it has no right to take and gratuitously care for patients who are able to pay for such service, or patients who are the wards of a wealthy corporation like the consolidated railroad and who receive medical and surgical attention at its expense." The editorial ends with this reflection: "Even a physician sometimes tires of doing gratuitous work which receives inadequate recognition."

Fifty Years Ago
(May, 1942)

The lead scientific contribution is by Charles Geschickter, MD who writes on neoplastic and related conditions in the bones of children. The author first notes that the frequency of inflammatory conditions of bone, in childhood, has been reduced drastically during the last decade, and ac-

cordingly, the relative frequency of bone neoplasms has increased. His learned discussion begins with the etiology, presenting clinical features and therapy of acute and chronic osteomyelitis (including those of syphilitic and tuberculous origin). He next dwells on Schuller-Christian's disease and Gaucher's disease and non-infectious metabolic disorders. Amongst neoplasms he provides the clinical profiles of osteochondromas, benign chondromas, benign bone cysts, Ewing's sarcoma, osteogenic sarcoma and secondary malignancies of bone. Finally, he briefly describes sacrococcygeal chordomas.

Merril Moore, MD provides a note on alcoholism. In reflecting upon the complexities of alcoholism, he asks the question: "Are alcoholics the same genetically as other people?" The answer, he says is that they probably are. There is no satisfactory evidence that alcoholism is hereditary. Alcoholism may have its roots, however, in childhood. The problem drinker was usually a problem child. The problems of acute alcoholics are the problems of head injury, exposure or immersion, with a high frequency of pneumonia. "What happens to alcoholics?" By now, the answer may be fairly clear. Alcoholics are subject to specific difficulties of their own which lead them to drink to excess, to special complications resulting from drinking to excess, and to a whole set of social maladjustments that are peculiar to them. It is to be hoped now, and in the future, that one more thing will happen to them: namely, that they will be studied, and that an attempt will be made to treat them scientifically and humanely as sick persons. If this is done, it is quite likely that some progress can be made towards the goal of preventing or controlling this serious public health problem.

A paper on scrotal cancer is presented by Peter Pineo Chase, MD (editor of the *Rhode Island Medical Journal*). After citing the remarkable insights of Percival Pott, the great physician of St Bartholomew's in London who in 1775 wrote a memorable paper on chimney sweeper's cancer, Chase describes the recent cases in the Rhode Island Hospital clinic. The third patient had been a fireman and was exposed to excessive amounts of soot and coal dust.

Eric Stone, MD writes on recent trends in the care of prostatic malignancy. The author notes that 20% of cases develop metastases before the growth has reached sufficient size to cause the symptoms of urinary tract obstruction. When metastases have appeared, the approach requires, first, that the urinary tract be made patent, then to implant radon seeds in the residual prostate and employ deep X-ray therapy for the metastases. Orchidectomy has also been of great benefit but the use of gonadotrophic hormones is still debated.

An editorial entitled "Speed Up" informs the reader of the procurement and assignment efforts originating in Washington to recruit physicians for the expanding armed forces. The Army proposes 5,000 new medical officers be commissioned within the next few months, and 14,000 more within the next seven moths. MDs up to the age of 45 years are eligible for commission.

The following physicians were selected as speakers for the 131st Annual Meeting of the Rhode Island Medical Society: Herman Pitts, MD, Robert Kennedy, MD, Timothy Leary, MD, Frank B Cutts, MD, Arthur Ruggles MD, Frederic Hussey, MD, Edward Churchill, MD, and Halsey DeWolf, MD.

Twenty-Five Years Ago
(May, 1967)

Francis D Lamb, MD, William E McKenney, MD and Oswaldo Velis, MD report on the first 74 cases of acute myocardial infarction cared for in the intensive and coronary care unit of Kent County Memorial Hospital from June 1, 1965 through September 30, 1966. After a detailed description of the care rendered and the statistics compiled, the authors conclude: Early and vigorous treatment of arrhythmias, using currently accepted drugs such as digitalis, lidocaine, and Pronestyl, and such procedures as prompt electrical conversion or transvenous pacing as the case may warrant, is of great importance. Such an approach will prevent many seeming benign disorders, such as premature contraction, minimal failure, and early degrees of block from becoming lethal. The Unit Director should promulgate accepted methods of treatment in the unit. We feel . . . that such units offer superior care to the coronary patient. We feel also that as therapy becomes better crystallized such facilities will lead the way to improved salvage in cases complicated by shock and decompensation.

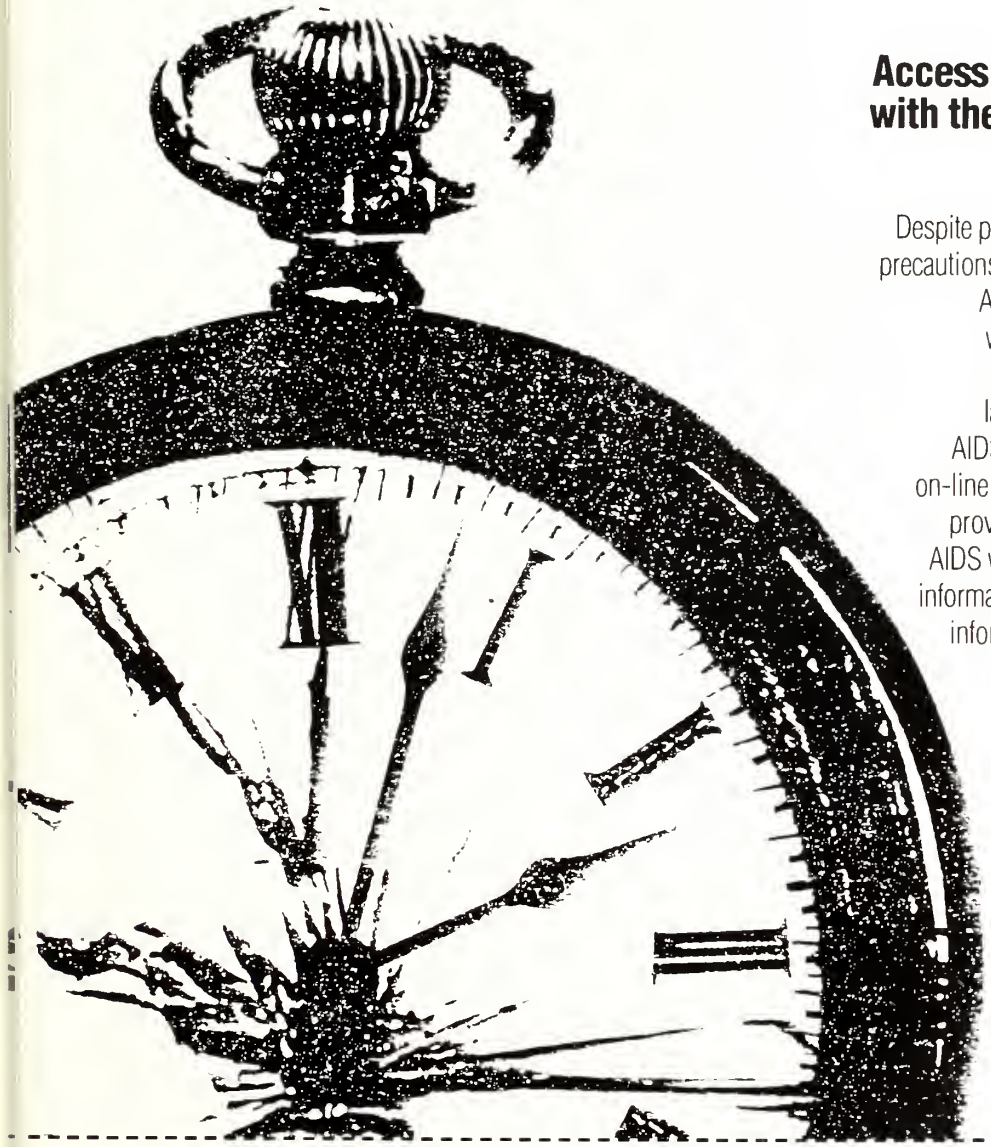
Mary Lekas, MD presents a paper entitled Permanent Tracheostomy in Chronic Obstructive Pulmonary Emphysema. She summarizes: Patients with chronic pulmonary disease who are unable to clear their airways, are subject to acute bouts of respiratory inadequacy often requiring tracheostomy and aspiration of secretion. This is the case history of an 84-year-old man who cleverly devised a Teflon plug with plastic apron to solve problems associated with his permanent tracheal stoma.

Robert T. Corwin, MD provides a progress note on the early detection of severe congenital heart disease in infancy. He notes: With the knowledge that most deaths from heart failure in congenital heart disease occur during the early moths of life, that palliative procedures can be performed to alleviate hypoxemia and control heart failure, and that the risks of diagnostic and operative procedures are increased in the symptomatic patient, it is essential that these infants be detected early and referred to diagnostic centers as soon as possible for specialized attention.

Charles F. Jones, MD, Daniel Liang, MD, and Raymond E. Moffitt, MD describe the case of a 28-year-old female with polyglandular endocrine adenomatosis presenting as hyperaldosteronism.

An editorial urges the enactment of state legislation governing motorcycle operation, and particularly recommending that there be specific licensing for motorcycles, and that cyclists be required to wear helmets.

Timely Information When Seconds Are Like Hours in the Fight Against AIDS...



Access AIDS information in seconds with the on-line services of the NLM

AIDS is everywhere.
Despite public service educational programs on safety precautions and AIDS awareness, the AIDS crisis rages. As AIDS research makes advances around the world, rapid access to that knowledge is vital. *The National Library of Medicine,* the world's largest medical library, offers you this access. AIDSLINE™, AIDSTRIALS, and AIDSDRUGS are on-line databases that provide educators, healthcare providers, scientists, and all others involved with AIDS with the most comprehensive and up-to-date information on AIDS. These unique sources contain information on literature, AIDS clinical trials, and agents being tested—in minutes.

When time is critical, the NLM makes every second count. For complete medical information around the clock...

FRIENDS OF THE NLM NATIONAL LIBRARY OF MEDICINE

For further information about the AIDS Information Services of the NLM, just fill out this coupon. Clip and mail to:

The National Library of Medicine
Public Information Office
Bethesda, Maryland 20894

Merck Company Foundation

Development of this public service message made possible by a grant from The Merck Company Foundation.

☐ Please send me more information about the NLM's AIDS Information Service
☐ Please send me more information about the Friends of the National Library of Medicine

Name _____

Title _____

Address _____

City _____ State _____ ZIP _____

Telephone No. _____

I saw this ad in _____
(name of publication)

Where can you find medical specialty/professional association statements and/or guidelines on delineation of hospital medical staff and clinical privileges?

In the **new** *Statements on Delineation of Hospital Privileges.*

Published by the American Medical Association (AMA) in November 1991, this up-to-date reference conveniently compiles 27 medical society/professional association statements and/or guidelines on delineation of hospital medical staff and clinical privileges into a single volume. It's an essential source of information for hospital medical staffs and administrators, credentials review committees, and medical societies.

Order now. Each 384-page volume costs only $14 for AMA members and $18 for nonmembers. Call 800 621-8335 and request item OP031191 or complete and return the attached Order Form.

Clip here.

Yes! Send me *Statements on Delineation of Hospital Privileges,* (OP031191), an essential 384-page, soft-bound book listing medical society/ professional association statements and/or guidelines on delineation of hospital medical staff and clinical privileges.

Name (Please Print) _____

Title _____ Organization _____

Address _____

City _____ State _____ Zip _____

Daytime phone number _____

AMA membership number _____ (Required for discount)

Enclosed is my check payable to: American Medical Association.
Please charge my Visa American Express MasterCard Optima

Account number _____ Expiration date _____

Cardholder's signature _____

Overnight Delivery Available!

____Copies @ $14 each (AMA member)	$ _____
____Copies @ $18 each (Nonmember)	$ _____
Subtotal	$ _____
Sales tax (see chart below.)	$ _____
Please add $3.50 shipping and handling for order totalling less than $35.00	$ _____
For overnight delivery, please add $15.00	$ _____
Total	$ _____

Tax Exempt Organizations — please enclose a copy of your certificate.

To order by phone, call 800 621-8335. (Visa, American Express, MasterCard, Optima)

Send this order form to: American Medical Association, Order Dept., OP031191, PO Box 109050, Chicago, IL 60610

Sales Tax Chart (May vary by county)

AZ 6.7%	IA 4%	ND 6.5%	TN 7.75%
AR 6%	ID 5%	NE 6.5%	WA 8.1%
CA 7.28%	IL 8%	NV 6%	WI 5.5%
CT 8%	KS 6.25%	NY 8.25%	WV 6%
DC 6%	MN 6.6%	OH 7%	
GA 6%	NC 6%	SC 5%	

American Medical Association
Physicians dedicated to the health of America

Priority Code JP001

INFORMATION FOR AUTHORS

Manuscripts: Manuscripts will be accepted for consideration with the understanding that they are original contributions, have never been published or submitted elsewhere, and are submitted only to the *Rhode Island Medical Journal.*

Specifications: Manuscripts must be original typed copy (not all capitals) on 8½ × 11 inch firm typewritten paper, double-spaced throughout (including title page, text, acknowledgments, and references) with margins of at least one inch and using but one side of each page. Tables, charts, and legends should be submitted separately from the text, and referred to by number (ie, Fig. 1) within the text. Subheadings must be inserted at reasonable intervals to break the typographic monotony of the text. Pages must be numbered consecutively. Italics and boldface print are never used except as subheadings.

Abbreviations: The *Journal* attempts to avoid the use of jargon and abbreviations. All abbreviations, especially of laboratory and diagnostic procedures, must be identified in the text.

Title Page: All manuscripts must include a title page which provides the following information: (1) a concise and informative title; (2) the name of the author or authors with their highest academic degree (ie, MD, PhD); (3) a concise biographical description for each author which includes specialty, practice location, academic appointment, and primary hospital affiliation; (4) mailing address and office telephone of principal author; (5) mailing address of author responsible for correspondence or reprint requests; (6) source of support if applicable.

Illustrations: Authors are urged to use the services of professional illustrators and photographers. Drawings and charts should always be done in black ink on white paper. Clear, black and white 5×7 glossy photographs should be submitted, and such illustrations numbered consecutively and their positions indicated in the text. Original magnifications should be noted. Illustrations defaced by handwriting or excessive handling will not be accepted. The figure number, indication of the top, and the name of the author must be attached to the back of each illustration. Legends for illustrations should be typewritten on a single list, with the numbers corresponding to those on photographs and drawings. Recognizable photographs of patients are to be appropriately masked and must carry with them written permission for publication. Special arrangements must be made with the editors for excessive numbers of illustrations. Color plates are not acceptable.

Identification of Patients: Names, initials should not be used. Use of numbers is a preferable form of identification.

Reprints: Because of cost considerations, reprints are not provided routinely to the author(s). Reprints may be ordered separately (100 copies minimum order) and printing costs will be charged to the author(s).

Responsibility: Manuscripts are subject to editorial revisions as deemed necessary by the editors and such modifications will be undertaken so as to bring them into conformity with *Journal* style, which is in compliance with the editorial standards of the AMA. However, neither the editors, nor the publishers, nor the Rhode Island Medical Society will accept responsibility for statements made or opinions expressed by any contributor in any article or feature published in the pages of the *Journal.*

Permission: When material is reproduced from other sources, full credit must be given both to the author and publisher of these sources. Where work is reported from a governmental service or institution, clearance by the appropriate authority must accompany the manuscript.

References: To conserve space and expense, references should be limited to those essential to the subject. The editor reserves the right to reduce the number when it is deemed necessary. The references must be double-spaced and numbered as they appear consecutively in the text, with their positions clearly indicated in the text. All references must be checked to assure complete accuracy. Each journal reference must include the full name of the author(s); complete title of paper; name of publication; volume number; issue number; first and last page of paper; and date (year, month, and day as indicated). Each book reference must include the full name of author(s), editor(s), or both, with initials; title of book; edition; publisher; location; year of publication, volume (if given); and page number. If the reference is to a chapter within a book, the author of the chapter, if different than the author of the book, and the title of the chapter (if any) must be provided.

Correspondence: All correspondence relating to publication should be addressed to: Managing Editor, *Rhode Island Medical Journal,* 106 Francis Street, Providence, RI 02903.

For the many faces of mild hypertension

MILD

THE MOST WIDELY USED CALCIUM ANTAGONIST AS MONOTHERAPY FOR MILD HYPERTENSION[1]*

- Effective 24-hour control
- Single-agent efficacy
- Well tolerated
- No adverse effects on [illegible]

ONCE-DAILY Calan® SR verapamil HCl

*The recommended starting dose for Calan SR is 180 mg once daily. Dose titration will be required in some patients to achieve blood pressure control. A lower initial starting dosage of 120 mg/day may be warranted in some patients (eg, the elderly, patients of small stature). Dosages above 240 mg daily should be administered in divided doses. Calan SR should be administered with food.

†Constipation, which is easily managed in most patients, is the most commonly reported side effect of Calan SR.

‡Verapamil should be administered cautiously to patients with impaired renal function.

References: 1. Data on file, Searle. 2. Edmonds D, Würth JP, Baumgart P, et al. Twenty-four-hour monitoring of blood pressure during calcium antagonist therapy. In: Fleckenstein A, Laragh SH, eds. *Hypertension—the Next Decade. Verapamil in Focus*. New York, NY: Churchill Livingstone; 1987:94-100. 3. Midtbø KA. Effects of long-term verapamil therapy on serum lipids and other metabolic parameters. *Am J Cardiol*. 1990;66:131-151. 4. Fagher B, Henningsen N, Hulthén L, et al. Antihypertensive and renal effects of enalapril and slow-release verapamil in essential hypertension. *Eur J Clin Pharmacol*. 1990;39(suppl 1):S41-S43. 5. Schmieder RE, Messerli FH, Garavaglia GE, et al. Cardiovascular effects of verapamil in patients with essential hypertension. *Circulation*. 1987;75:1030-1036. 6. Midtbø K, Lauve O, Hals O. No metabolic side effects of long-term treatment with verapamil in hypertension. *Angiology*. 1988;39:1025-1029.

BRIEF SUMMARY

Contraindications: Severe LV dysfunction (see *Warnings*), hypotension (systolic pressure < 90 mm Hg) or cardiogenic shock, sick sinus syndrome (if no pacemaker is present), 2nd- or 3rd-degree AV block (if no pacemaker is present), atrial flutter/fibrillation with an accessory bypass tract (eg, WPW or LGL syndromes), hypersensitivity to verapamil.

Warnings: Verapamil should be avoided in patients with severe LV dysfunction (eg, ejection fraction < 30%) or moderate to severe symptoms of cardiac failure and in patients with any degree of ventricular dysfunction if they are receiving a beta-blocker. Control milder heart failure with optimum digitalization and/or diuretics before Calan SR is used. Verapamil may occasionally produce hypotension. Elevations of liver enzymes have been reported. Several cases have been demonstrated to be produced by verapamil. Periodic monitoring of liver function in patients on verapamil is prudent. Some patients with paroxysmal and/or chronic atrial flutter/fibrillation and an accessory AV pathway (eg, WPW or LGL syndromes) have developed an increased antegrade conduction across the accessory pathway bypassing the AV node, producing a very rapid ventricular response or ventricular fibrillation after receiving I.V. verapamil (or digitalis). Because of this risk, oral verapamil is contraindicated in such patients. AV block may occur (2nd- and 3rd-degree, 0.8%). Development of marked 1st-degree block or progression to 2nd- or 3rd-degree block requires reduction in dosage or, rarely, discontinuation and institution of appropriate therapy. Sinus bradycardia, 2nd-degree AV block, sinus arrest, pulmonary edema and/or severe hypotension were seen in some critically ill patients with hypertrophic cardiomyopathy who were treated with verapamil.

Precautions: Verapamil should be given cautiously to patients with impaired hepatic function (in severe dysfunction use about 30% of the normal dose) or impaired renal function, and patients should be monitored for abnormal prolongation of the PR interval or other signs of overdosage. Verapamil may decrease neuromuscular transmission in patients with Duchenne's muscular dystrophy and may prolong recovery from the neuromuscular blocking agent vecuronium. It may be necessary to decrease verapamil dosage in patients with attenuated neuromuscular transmission. Combined therapy with beta-adrenergic blockers and verapamil may result in additive negative effects on heart rate, atrioventricular conduction and/or cardiac contractility; there have been reports of excessive bradycardia and AV block, including complete heart block. The risks of such combined therapy may outweigh the benefits. The combination should be used only with caution and close monitoring. Decreased metoprolol and propranolol clearance may occur when either drug is administered concomitantly with verapamil. A variable effect has been seen with combined use of atenolol. Chronic verapamil treatment can increase serum digoxin levels by 50% to 75% during the first week of therapy, which can result in digitalis toxicity. In patients with hepatic cirrhosis, verapamil may reduce total body clearance and extrarenal clearance of digitoxin. The digoxin dose should be reduced when verapamil is given, and the patient carefully monitored. Verapamil will usually have an additive effect in patients receiving blood-pressure-lowering agents. Disopyramide should not be given within 48 hours before or 24 hours after verapamil administration. Concomitant use of flecainide and verapamil may have additive effects on myocardial contractility, AV conduction, and repolarization. Combined verapamil and quinidine therapy in patients with hypertrophic cardiomyopathy should be avoided, since significant hypotension may result. Concomitant use of lithium and verapamil may result in a lowering of serum lithium levels or increased sensitivity to lithium. Patients receiving both drugs must be monitored carefully. Verapamil may increase carbamazepine concentrations during combined use. Rifampin may reduce verapamil bioavailability. Phenobarbital may increase verapamil clearance. Verapamil may increase serum levels of cyclosporin. Verapamil may inhibit the clearance and increase the plasma levels of theophylline. Concomitant use of inhalation anesthetics and calcium antagonists needs careful titration to avoid excessive cardiovascular depression. Verapamil may potentiate the activity of neuromuscular blocking agents (curare-like and depolarizing), dosage reduction may be required. There was no evidence of a carcinogenic potential of verapamil administered to rats for 2 years. A study in rats did not suggest a tumorigenic potential, and verapamil was not mutagenic in the Ames test. Pregnancy Category C. There are no adequate and well-controlled studies in pregnant women. This drug should be used during pregnancy, labor, and delivery only if clearly needed. Verapamil is excreted in breast milk; therefore, nursing should be discontinued during verapamil use.

Adverse Reactions: Constipation (7.3%), dizziness (3.3%), nausea (2.7%), hypotension (2.5%), headache (2.2%), edema (1.9%), CHF, pulmonary edema (1.8%), fatigue (1.7%), dyspnea (1.4%), bradycardia: HR < 50/min (1.4%), AV block: total 1°,2°,3° (1.2%), 2° and 3° (0.8%), rash (1.2%), flushing (0.6%), elevated liver enzymes, reversible non-obstructive paralytic ileus. The following reactions, reported in 1.0% or less of patients, occurred under conditions where a causal relationship is uncertain: angina pectoris, atrioventricular dissociation, chest pain, claudication, myocardial infarction, palpitations, purpura (vasculitis), syncope, diarrhea, dry mouth, gastrointestinal distress, gingival hyperplasia, ecchymosis or bruising, cerebrovascular accident, confusion, equilibrium disorders, insomnia, muscle cramps, paresthesia, psychotic symptoms, shakiness, somnolence, arthralgia and rash, exanthema, hair loss, hyperkeratosis, macules, sweating, urticaria, Stevens-Johnson syndrome, erythema multiforme, blurred vision, gynecomastia, galactorrhea/hyperprolactinemia, increased urination, spotty menstruation, impotence.

4/11/91 • P91CA6277V

Address medical inquiries to:
G.D. Searle & Co.
Medical & Scientific
Information Department
4901 Searle Parkway
Skokie, IL 60077

© 1992 Searle

A92CA6694T

SEARLE

G.D. Searle & Co.
Box 5110, Chicago, IL 60680

FRANCIS A COUNTWAY LIB OF MED
EXCHANGE OFFICE
10 SHATTUCK STREET
BOSTON MA 02115

RHODE ISLAND MEDICINE

June 1992

Volume 75, Number 6

Clinical Observations in Rhode Island

Does your collection agency eat too much?

Most collection agencies demand an up-front fee for their services. Then they charge you again when they collect. With Rossi Law Offices, Ltd., you pay no fee unless we are successful. Why? Because we concentrate exclusively on collections, combining the power of a law firm with the computerized efficiency of a collection agency. We can not only ask for payment, we can legally compel it through litigation, so our chances of collecting are much greater. If you're feeding your collection agency too many dollars, call us at 401-438-8660 for a free consultation.

ROSSI LAW OFFICES, LTD.
a collection law group

124 Taunton Avenue, PO Box 14547, East Providence, RI 02914

RI and MA have no procedure for certification of any specialty in the practice of law

RHODE ISLAND MEDICINE

Publication of the Rhode Island Medical Society

LIBRARY OF MEDICINE
JUN 1992

EDITORIAL STAFF

Stanley M. Aronson, MD
Editor-in-Chief

Anne M. Christner, PhD
Managing Editor

Hugo Taussig, MD
Book Review Editor

Seebert J. Goldowsky, MD
Editor-in-Chief Emeritus

John P. Sullma
Production Editor

Betsy Hunt
Advertising Manager

EDITORIAL BOARD

*Edward R. Feller, MD
Chairman

*Joseph Amaral, MD

*Stanley M. Aronson, MD

Edward M. Belser, PhD, JD

Paul Calabresi, MD

*Richard A. Carleton, MD

Margaret Cololan, MSJ

*James P. Crowley, MD

*Peter A. Holmann, MD

*Marguerite A. Neill, MD

*Frank J. Schaberg, Jr., MD

*Fred J. Schiffman, MD

William J. Waters, Jr., PhD

*Member of Publications Committee

OFFICERS

Kathleen C. Hittner, MD
President

Robert E. Baute, MD
President-Elect

A. Robert Buonanno, MD
Secretary

Frances P. Conklin, MD
Treasurer

Richard Wong, MD
Immediate Past President

DISTRICT AND COUNTY PRESIDENTS

Fred Vohr, MD
Bristol County Medical Society

William F. Coscina, MD
Kent County Medical Society

Orest Zaklynsky, MD
Newport County Medical Society

David P. Carter, MD
Pawtucket Medical Association

Michael B. Macko, MD
Providence Medical Association

Joseph R. Dotolo, MD
Washington County Medical Society

Patrick R. Levesque, MD
Woonsocket District Medical Society

Volume 75, Number 6 June 1992

TABLE OF CONTENTS

COMMENTARIES

290 Gauging the Fevered Brow

291 The Language of Epidemiology (XII.) Meta-Analysis, Studying Studies
Edward R. Feller, MD

CONTRIBUTIONS
Clinical Observations in Rhode Island

297 **Colorectal Carcinoma in Rhode Island: Clinical Experience with 841 Cases**
Clarence H. Soderberg, Jr, MD
J. Robert Bowen, MD
Brian A. Dorman, MD
John C. Pezzullo, PhD
Thomas K. Shahinian, MD
William R. Thompson, MD

303 **Carpal Tunnel Syndrome: A Review**
Arnold-Peter C. Weiss, MD
Edward Akelman, MD

309 **Immune Neutropenia and Pregnancy**
Joseph R. Salvatore, MD
Alan Weitberg, MD

313 **Transfer from Animal to Human Insulin: A Clinical Experience**
Charles B. Kahn, MD
R. Preston Lamberton, MD
Dennis S. Krauss, MD

317 **Radon: Health Implications in Rhode Island**
Richard V. Morgera, MD

COLUMNS

320 **HEALTH BY NUMBERS**
Decline in Cigarette Smoking Among Rhode Island Women

323 **CONTEMPORARY PROBLEMS IN MEDICINE**
Impartial Medical Evaluation
Henry B. Litchman, MD

329 **THE RHODE ISLAND MEDICAL JOURNAL HERITAGE**

Cover: An 1845 lithograph by Honoré Daumier

Rhode Island Medicine is owned and published monthly by the Rhode Island Medical Society, 106 Francis Street, Providence, Rhode Island 02903, Ph: 401-331-3207. Single copies $2.00 — Subscriptions $20.00 per year (members of the Rhode Island Medical Society — $5.00 annually). Published articles represent opinions of the authors and do not necessarily reflect the official policy of the Rhode Island Medical Society unless clearly specified. Advertisements do not imply sponsorship or endorsement by the Rhode Island Medical Society. Second class postage paid at Providence, Rhode Island. **ISSN 1061-222X.** POSTMASTER: Send address changes to RHODE ISLAND MEDICINE, 106 Francis Street, Providence, RI 02903. National Advertising Bureau: State Medical Journal Advertising Bureau, Inc., 711 South Blvd., Oak Park, Illinois 60302. Phone 708-383-8800.

COMMENTARIES

Gauging the Fevered Brow

Despite impressive technical advances, the simple clinical thermometer has not been supplanted and remains one of the more enduring symbols of clinical medicine. It is likely that this fragile cylinder of glass yields more utilitarian information than any other portable piece of diagnostic equipment. No nursing note is considered complete unless the patient's temperature has been duly recorded. Physicians, today, may be classified into two camps; those who think in the Fahrenheit scale (generally those older than 55) and those who think directly in the centigrade (Celsius) scale without secretly converting the value to, what to them is, the more comprehensible Fahrenheit value. But regardless of which scale is employed, no clinician disregards the numeric values. Fever, said Galen, is the scream of deep illness seeking attention.

Where did this handy contrivance called the thermometer come from, and when did it become an everyday resource of medicine in measuring increased body temperature?

Fever, unquantified, has always been a cardinal herald of systemic illness. Ancient texts reached beyond the mere presence or absence of fever and designed an elaborate taxonomy of fever profiles without necessarily seeking out their etiologies. Fevers were distinguished as eruptive, remitting, cerebral, relapsing, intermittent, quotidian, continued, or hectic, to name but a few. On the other hand, Biblical references to fever, at least of the physiological kind, are quite meager; when they are found they seem to represent divine retribution rather than natural illness. Deuteronomy 28:22 states: "The Lord will smite you with consumption and with fever, inflammation and fiery heat . . ." Again in Leviticus 26:16, "I will do this to you: I will appoint over you sudden terror, consumption, and fever that waste the eyes and cause life to pine away."

When the fever rages and the pulse accelerates, a measuring instrument certainly is not required. But, asked the physicians of the 17th century, might there be trifling increments of fever – low-grade perhaps – that only an objective instrument might identify? And further, when there is an absence of internal disease, there must always be some stable level of body heat which can be regarded as normal and which should stand as a criterion against which morbid states may be measured.

Predictably, two groups of 17th century scientists advanced the development of a reliable means for the testing of ambient heat – the meteorologists and the physicians. Heat was one of the last of the natural qualities to be calibrated in a formal manner. Heat, in contrast to mass or volume, is not an additive attribute. Combining two liters of water, one at 30°C and one at 50°C yields a mixture of 40°C not 80°C. The Aristotelians talked freely of heat and cold but assigned no numeric value to the amounts of either. To them, it seemed sufficient to observe that one object was warmer or colder than another. Galen, more quantitatively oriented, suggested four levels of temperature with the midpoint being an equal mixture of boiling water and ice.

In creating an instrument to measure heat, it is essential that the candidate thermometer do two things: it must respond consistently (and quickly) to changes in surrounding temperature, and it must possess some built-in scale that will provide a numeric value for each thermic variation. In short, it must offer reliable information.

The initial design of a thermometer arose from two established observations: (1) the volume of a substance expands when heated; and (2) bodies next to each other equilibrate in temperature. The first of many problems, then, was to select the thermometric substance. It should possess the following qualities: it undergoes significant expansion per unit of heat introduced; and the volumetric increase caused by introduced amounts of heat shall be about the same whether in the cold or warm temperature range.

The discovery of a functioning, reliable thermometer was not a sudden epiphany but rather a steady sequence of imaginative steps over two centuries of investigative labor. Most historic texts (eg, WEK Middleton's *History of the Thermometer*, Johns Hopkins Press, 1966) give initial discovery credit to an obscure Venetian physician, Santorio Santorre. In 1611 he was appointed as professor of medicine in Padua and while there sought ways of adapting objective measurements to the sick patient. He recorded his experiments in the measurement of air temperature with an instrument of his personal devising. His novelty, as he called it, was capable of measuring body heat, but only with great difficulty. Because it had no objective scale, it was called a thermoscope rather than a thermometer. It consisted of a globe containing air, with a tubular extension suspended inferiorly into a container of water (Figure 1). When the air within the globe was heated, it expanded and depressed the water-level within the tube. Similarly, when the air volume within the globe contracted, the water

level within the tube of glass rose. (This is contrary to the movements of contemporary thermometers where increased heat causes the thermometric level to rise.) The instrument was crude, not very mobile, had no objective scale, and its design was flawed by the fact that the fluid in the lower chamber was exposed to the air; thus, in passing, it acted also as a barometer deviating the column of water regardless of the ambient temperature. Dyes were then added to the water in Santorre's instrument to make the vertical column of fluid more visible. Since water froze below a certain temperature, wine was then substituted because it was both colored and possessed a much lower freezing point. Instruments such as Santorre's were referred to as air thermoscopes because the responding substance was air.

The Royal Society in London took on the task of improving the instrument and a succession of great British scientists devoted much of their time to this task (eg, Newton, Boyle, Hook, Wren, Halley, Locke.) In 1663 they constructed a thermometer and used it to calibrate others. But fine as it was, it still lacked an essential feature: the scale was arbitrary and could not be employed anywhere but in London.

The barometric flaw in the air thermoscope was soon recognized and a sealed instrument was then designed. The expanding-contracting substance

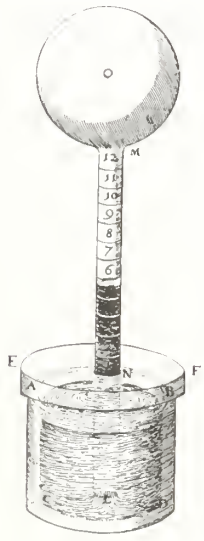


Fig.1–Santorre's 17th century "thermoscope"

was now a liquid, usually a vintage wine, hence the name, spirit thermometer. Fixed points were sought after, using normal body temperature, the freezing point of distilled water, the melting point of distilled water and the boiling point of distilled water as referents. It was the Italian scientist Renaldini (1694) who recognized the thermometric constancy of melting ice rather than freezing water, an essential step in establishing accurately fixed points on the thermometer.

Daniel Fahrenheit was born in Danzig in 1686 but lived much of his life in western Europe, particularly the Netherlands. He was a physicist and instrument-maker who constructed a thermometer using liquid mercury. He was not, however, the first to use this substance. He devised a scale such that the melting of ice was defined as 32° and the boiling point of distilled water as 212°. With this finely crafted instrument, with a uniform bore of the tube, there was now ample room to measure temperatures below freezing and well above the boiling point of water.

The other name closely associated with thermometric notation is that of Anders Celsius, the 18th century Swedish astronomer. He initially chose to assign the value of 100 to the melting of distilled water and zero to boiling water, both calibrated at sea-level to diminish the barometric effects on the boiling point of water. His close friend and colleague, the physician-botanist Carl Linnaeus, suggested that this scalar notation was counter-intuitive and should therefore be reversed. It is only 44 years ago that "degrees centigrade" had been changed to "degrees Celsius."

The portable body-cavity thermometer that held its highest reading (by virtue of a stenosis in the inner bore) was invented in the early 19th century. Since then, improvements in the instrument have been negligible. During this century, it has been imbued with great authoritative powers. Most American families possess a thermometer and use it frequently as the sole criterion of health or sickness in their children. Rosten tells the story

Fig. 2–An early thermometer

of the physician who asks: "What are you taking for that terrible fever?" And the patient responds: "Make me an offer."

Stanley M. Aronson, MD

The Language of Epidemiology (XII.): Meta-Analysis, Studying Studies

When different studies yield conflicting or imprecise results, a problem in interpretation arises. Meta-analysis is a relatively new technique that analyzes and combines quantitative results from a number of independent, previously published research efforts in order to achieve a more stable and accurate estimate of outcome – an estimate that could not have been obtained from any single one of the independent studies.

Purpose and Utility: Some clinical trials may have had an inadequate sample size of patients to provide reliable answers. Meta-analysis then may be useful in a variety of ways. It may:

1. Resolve uncertainty when studies disagree or results are unclear, eg,

radiotherapy or no radiotherapy in treating a particular cancer.

2. Improve statistical power for outcome measures by the increased sample size of multiple studies.

3. Explore new questions not addressed during the original trials.

4. Provide insights on why and how different studies yield conflicting results (Different types of patients? Different doses or regimens? Different study endpoints?).

5. Improve research methodology by assessing the strengths and weaknesses in a particular research area. (For example, in studying survival data after acute myocardial infarction, do the different studies define infarction differently? Does one include studies before the establishment of coronary care units or the availability of antiarrhythmics? And how does one compare or examine studies with or without the use of anticoagulants?)

Meta-Analysis Design: The methods by which a meta-analysis of clinical problems is conducted must be rigorous and explicitly stated. Combining the results of different studies must be valid and meaningful by both methodological and clinical criteria. The following specifics must be observed:

1. A literature search must include all relevant trials.

2. Trials analyzed and rejected must be listed.

3. Methods used in different trials must be outlined.

4. The range of patient characteristics, diagnoses, and treatment regimens must be listed to allow the reader to assess the validity and generalizability of the analysis. In a meta-analysis of radiotherapy in a particular cancer, for example, are the doses the same? Are the patients similar in stage of the disease and the choice of diagnostic criteria?

5. Guidelines must be provided to determine why certain studies – and not others – are deemed appropriate for inclusion in the meta-analysis.

6. Statistical methods used must be carefully described.

Bias and Methodological Problems: It has been stated that "pooling" data from different studies (when patients, methods and treatments are sufficiently dissimilar) will result in "drowning" the results in misleading conclusions. If the disparity in separate trials is too great to have arisen by chance, then trial results should not be pooled. The conclusions of a meta-analysis are valid only if the pooling of historic data satisfies certain established qualitative and quantitative criteria.

In the real world of treating living patients, the best guide may be studies conducted in patients most similar to our patient, rather than depending upon combined historical data.

Meta-analysis is prone to systematic errors in collecting and interpreting data. Because the research worker decides which historical studies to include, selection bias may arise. Similarly, when a multitude of studies evaluate many subgroups, endpoints and exclusion criteria, meta-analysis may differ in interpreting separate data (data extraction bias). Negative studies, those finding no benefit for a particular treatment, for example, are less likely to be published. Any subsequent evaluation of pooled studies might thus be flawed (publication bias).

The Promise and the Challenge: Great statistical power may be achieved by combining previously published research. The uncertainty of hazy or conflicting results in a particular field thus may be clarified. Meta-analysis is a current "darling" in both medical and social sciences and can be a powerful biostatistical instrument. Journals are now besieged with the first wave of meta-analysis of meta-analyses.

The reader should be aware, however, that the statistical assumptions and methodologies in such analyses are complex. This new class of scientific article may be less comprehensible to the reader schooled in the traditional review article or original research study. On-line databases may be incomplete, studies may be included or excluded on the basis of questionable criteria, and over-reliance on quantitative elements may obscure the essence of the area analyzed. This hybrid form of analysis is best considered as an evolving research strategy.

Edward R. Feller, MD

PHYSICIAN'S OFFICE
for LEASE

- High Service Avenue, North Providence
- Across from Fatima Hospital
- Near Bus Stop
- 2 Examination Rooms
- Large Consultation Room
- Waiting Room with Fireplace
- Business Office
- FURNISHED

Call: (401) 353-7373

For your older patients, Assisted Living can mean independence and security. Here's why.

1 They have their own apartment, yet help is always close at hand. Our professional, licensed nursing staff can assist as needed with bathing, dressing and administering medications. 2 They enjoy gracious dining three times daily, without the bother of shopping, cooking or cleaning up. Plus, our registered dietitians are available for personal consultation. 3 They have the freedom to pursue their own interests, yet have the security of nursing and emergency care around-the-clock. 4 They can stay near family and friends, because there's sure to be a Horizon Retirement Center that's so close to home.

There are a lot of reasons for your older patients to consider Assisted Living at Horizon, but enjoying independence and security is the one that really counts.

HORIZON
RETIREMENT CENTERS

West Bay Manor	Greenwich Bay Manor	South Bay Manor	North Bay Manor	East Bay Manor
Warwick 739-7300	E. Greenwich 885-3334	S. Kingstown 789-4880	Smithfield 232-5577	E. Providence/Barrington 433-5000

You treated little Johnny for measles in kindergarten, chicken pox in 3rd grade, mono in high school.

But what can you do for his HIV today?

People with HIV are special patients with specific needs. That's why it helps to have experience with HIV when treating an infected patient–the kind of experience doctors find at Clinical Partners.

Clinical Partners is a group of healthcare professionals dedicated to helping patients live with HIV. We are alone in the complete array of services we provide to physicians, employers and insurers of those living with HIV. Our early intervention averts costly hospital stays, while increasing patient care and support.

Operating successfully in Boston, New York and Los Angeles, Clinical Partners is pleased to announce the first anniversary of our Providence office, under the expert guidance of Linda Durand NP, RNC and Deborah Matson CISW, MSW.

We want Rhode Island physicians to know Clinical Partners is here to help, and here to stay. As the patient's primary physician, you can benefit from our knowledge and experience, which is available to help you treat HIV infection and AIDS.

To find out how Clinical Partners can be your partner in treating HIV patients, call our Providence office today at 454-8880 or 1-800-285-8880.

Clinical Partners

Helping people make choices about HIV.

The ACCUPRIL Single-Agent Commitment™

Parke-Davis is confident that for many of your hypertensive patients ACCUPRIL will achieve the decrease in blood pressure you expect.

If, in your medical judgment, your patient requires a diuretic in addition to ACCUPRIL at any time during ACCUPRIL therapy, Parke-Davis will refund your patient's cost of the diuretic.*†

ONCE-A-DAY‡

ACCUPRIL®™

quinapril HCl tablets 10, 20, 40 mg

* See DOSAGE AND ADMINISTRATION section of prescribing information.

† If, after an adequate trial of ACCUPRIL alone, based on your medical judgment as the prescribing physician, you determine that your patient requires the addition of a diuretic, Parke-Davis will refund to the patient his/her cost for the diuretic prescription less any amount reimbursed or paid for by an HMO, insurance company, or any other plan or program.

For more details, ask your Parke-Davis Representative or call 1-800-955-3077.

‡ In some patients, the antihypertensive effect may diminish toward the end of the once-daily dosing interval. In such patients, an increase in dosage or twice-daily administration may be warranted.

ACCUPRIL is available in 10, 20, and 40 mg tablets. Usual initial starting dosage is 10 mg once daily.

ACCUPRIL is contraindicated in patients who are hypersensitive to this product and in patients with a history of angioedema related to previous treatment with an ACE inhibitor.

Please see brief summary of prescribing information on following page.

© 1991 Warner-Lambert Company

PARKE-DAVIS

USE IN PREGNANCY

When used in pregnancy during the second and third trimesters, ACE inhibitors can cause injury and even death to the developing fetus When pregnancy is detected, ACCUPRIL should be discontinued as soon as possible See WARNINGS, Fetal/Neonatal Morbidity and Mortality

Before prescribing, please see full prescribing information A brief summary follows

INDICATIONS AND USAGE

ACCUPRIL is indicated for the treatment of hypertension It may be used alone or in combination with thiazide diuretics

In using ACCUPRIL, consideration should be given to the fact that another angiotensin-converting enzyme (ACE) inhibitor, captopril, has caused agranulocytosis, particularly in patients with renal impairment or collagen vascular disease Available data are insufficient to show that ACCUPRIL does not have a similar risk (see WARNINGS)

CONTRAINDICATIONS

ACCUPRIL is contraindicated in patients who are hypersensitive to this product and in patients with a history of angioedema related to previous treatment with an ACE inhibitor

WARNINGS

Angioedema: Angioedema of the face, extremities, lips, tongue, glottis, and larynx has been reported in patients treated with ACE inhibitors and has been seen in 0 1% of patients receiving ACCUPRIL Angioedema associated with laryngeal edema can be fatal If laryngeal stridor or angioedema of the face, tongue, or glottis occurs, treatment with ACCUPRIL should be discontinued immediately, the patient treated in accordance with accepted medical care, and carefully observed until the swelling disappears In instances where swelling is confined to the face and lips, the condition generally resolves without treatment, antihistamines may be useful in relieving symptoms **Where there is involvement of the tongue, glottis, or larynx likely to cause airway obstruction, emergency therapy including, but not limited to, subcutaneous epinephrine solution 1:1000 (0.3 to 0 5 mL) should be promptly administered (see ADVERSE REACTIONS).**

Hypotension: Symptomatic hypotension was rarely seen in uncomplicated hypertensive patients treated with ACCUPRIL but, as with other ACE inhibitors, it is a possible consequence of therapy in salt/volume depleted patients, such as those previously treated with diuretics or dietary salt restriction or who are on dialysis (see PRECAUTIONS, DRUG INTERACTIONS, and ADVERSE REACTIONS) In controlled studies, syncope was observed in 0 4% of patients (N = 3203), this incidence was similar to that observed for captopril (1%) and enalapril (0 8%)

In patients with concomitant congestive heart failure, with or without associated renal insufficiency, ACE inhibitor therapy may cause excessive hypotension which may be associated with oliguria or azotemia and, rarely, with acute renal failure and death In such patients, ACCUPRIL therapy should be started at the recommended dose under close medical supervision These patients should be followed closely for the first 2 weeks of treatment and whenever the dosage of antihypertensive medication is increased (see DOSAGE AND ADMINISTRATION)

If symptomatic hypotension occurs, the patient should be placed in the supine position and, if necessary, normal saline may be administered intravenously A transient hypotensive response is not a contraindication to further doses, however, lower doses of ACCUPRIL or reduced concomitant diuretic therapy should be considered

Neutropenia/Agranulocytosis: Another ACE inhibitor, captopril, has been shown to cause agranulocytosis and bone marrow depression rarely in patients with uncomplicated hypertension, but more frequently in patients with renal impairment, especially if they also have a collagen vascular disease such as systemic lupus erythematosus or scleroderma Agranulocytosis did occur during ACCUPRIL treatment in one patient with a history of neutropenia during previous captopril therapy Available data from clinical trials of ACCUPRIL are insufficient to show that, in patients without prior reactions to other ACE inhibitors, ACCUPRIL does not cause agranulocytosis at similar rates As with other ACE inhibitors, periodic monitoring of white blood cell counts in patients with collagen vascular disease and/or renal disease should be considered

Fetal/Neonatal Morbidity and Mortality: ACE inhibitors can cause fetal and neonatal morbidity and death when administered to pregnant women Several dozen cases have been reported in the world literature When pregnancy is detected, ACE inhibitors should be discontinued as soon as possible

The use of ACE inhibitors during the second and third trimesters of pregnancy has been associated with fetal and neonatal injury, including hypotension, neonatal skull hypoplasia, anuria, reversible or irreversible renal failure, and death Oligohydramnios has also been reported, presumably resulting from decreased fetal renal function; oligohydramnios in this setting has been associated with fetal limb contractures, craniotacial deformation, and hypoplastic lung development Prematurity, intrauterine growth retardation, and patent ductus arteriosus have also been reported, although it is not clear whether these occurrences were due to the ACE inhibitor exposure

These adverse effects do not appear to have resulted from intrauterine ACE inhibitor exposure that has been limited to the first trimester Mothers whose embryos and fetuses are exposed to ACE inhibitors only during the first trimester should be so informed Nonetheless, when patients become pregnant, physicians should make every effort to discontinue the use of ACCUPRIL as soon as possible

Rarely (probably less often than once in every thousand pregnancies), no alternative to ACE inhibitors will be found In these rare cases, the mothers should be apprised of the potential hazards to their fetuses, and serial ultrasound examinations should be performed to assess the intraamniotic environment

If oligohydramnios is observed, ACCUPRIL should be discontinued unless it is considered life-saving for the mother Contraction stress testing (CST), a non-stress test (NST), or biophysical profiling (BPP) may be appropriate, depending upon the week of pregnancy Patients and physicians should be aware, however, that oligohydramnios may not appear until after the fetus has sustained irreversible injury

Infants with histories of *in utero* exposure to ACE inhibitors should be closely observed for hypotension, oliguria, and hyperkalemia If oliguria occurs, attention should be directed toward support of blood pressure and renal perfusion Exchange transfusion or dialysis may be required as a means of reversing hypotension and/or substituting for disordered renal function Removal of ACCUPRIL, which crosses the placenta, from the neonatal circulation is not significantly accelerated by these means

No teratogenic effects of ACCUPRIL were seen in studies of pregnant rats and rabbits On a mg/kg basis, the doses used were up to 180 times (in rats) and one time (in rabbits) the maximum recommended human dose

PRECAUTIONS

General

Impaired renal function: As a consequence of inhibiting the renin-angiotensin-aldosterone system, changes in renal function may be anticipated in susceptible individuals In patients with severe heart failure whose renal function may depend on the activity of the renin-angiotensin-aldosterone system, treatment with ACE inhibitors, including ACCUPRIL, may be associated with oliguria and/or progressive azotemia and rarely acute renal failure and/or death

In clinical studies in hypertensive patients with unilateral or bilateral renal artery stenosis, increases in blood urea nitrogen and serum creatinine have been observed in some patients following ACE inhibitor therapy These increases were almost always reversible upon discontinuation of the ACE inhibitor and/or diuretic therapy In such patients, renal function should be monitored during the first few weeks of therapy

Some hypertensive patients with no apparent preexisting renal vascular disease have developed increases in blood urea and serum creatinine, usually minor and transient, especially when ACCUPRIL has been given concomitantly with a diuretic This is more likely to occur in patients with preexisting renal impairment Dosage reduction and/or discontinuation of any diuretic and/or ACCUPRIL may be required

Evaluation of hypertensive patients should always include assessment of renal function (see DOSAGE AND ADMINISTRATION)

Hyperkalemia and potassium-sparing diuretics: In clinical trials, hyperkalemia (serum potassium ≥5 8 mmol/L) occurred in approximately 2% of patients receiving ACCUPRIL In most cases, elevated serum potassium levels were isolated values which resolved despite continued therapy Less than 0 1% of patients discontinued therapy due to hyperkalemia Risk factors for the development of hyperkalemia include renal insufficiency, diabetes mellitus, and the concomitant use of potassium-sparing diuretics, potassium supplements, and/or potassium-containing salt substitutes, which should be used cautiously, if at all, with ACCUPRIL (see PRECAUTIONS, Drug Interactions)

Cough: Cough has been reported with the use of ACE inhibitors Characteristically, the cough is nonproductive, persistent, and resolves after discontinuation of therapy ACE inhibitor-induced cough should be considered as part of the differential diagnosis of cough

Surgery/anesthesia: In patients undergoing major surgery or during anesthesia with agents that produce hypotension, ACCUPRIL will block angiotensin II formation secondary to compensatory renin release If hypotension occurs and is considered to be due to this mechanism, it can be corrected by volume expansion

Information for Patients

Pregnancy: Female patients of childbearing age should be told about the consequences of second- and third-trimester exposure to ACE inhibitors, and they should also be told that these consequences do not appear to have resulted from intrauterine ACE-inhibitor exposure that has been limited to the first trimester These patients should be asked to report pregnancies to their physicians as soon as possible

Angioedema: Angioedema, including laryngeal edema, can occur with treatment with ACE inhibitors, especially following the first dose Patients should be so advised and told to report immediately any signs or symptoms suggesting angioedema (swelling of face, extremities, eyes, lips, tongue, difficulty in swallowing or breathing) and to stop taking the drug until they have consulted with their physician (see WARNINGS)

Symptomatic hypotension: Patients should be cautioned that lightheadedness can occur, especially during the first few days of ACCUPRIL therapy, and that it should be reported to a physician If actual syncope occurs, patients should be told to not take the drug until they have consulted with their physician (see WARNINGS)

All patients should be cautioned that inadequate fluid intake or excessive perspiration, diarrhea, or vomiting can lead to an excessive fall in blood pressure because of reduction in fluid volume, with the same consequences of lightheadedness and possible syncope

Patients planning to undergo any surgery and/or anesthesia should be told to inform their physician that they are taking an ACE inhibitor

Hyperkalemia: Patients should be told not to use potassium supplements or salt substitutes containing potassium without consulting their physician (see PRECAUTIONS)

Neutropenia: Patients should be told to report promptly any indication of infection (eg, sore throat, fever) which could be a sign of neutropenia

NOTE As with many other drugs, certain advice to patients being treated with ACCUPRIL is warranted This information is intended to aid in the safe and effective use of this medication It is not a disclosure of all possible adverse or intended effects

Drug Interactions

Concomitant diuretic therapy: As with other ACE inhibitors, patients on diuretics, especially those on recently instituted diuretic therapy, may occasionally experience an excessive reduction of blood pressure after initiation of therapy with ACCUPRIL The possibility of hypotensive effects with ACCUPRIL may be minimized by either discontinuing the diuretic or cautiously increasing salt intake prior to initiation of treatment with ACCUPRIL If it is not possible to discontinue the diuretic, the starting dose of quinapril should be reduced (see DOSAGE AND ADMINISTRATION).

Agents increasing serum potassium: Quinapril can attenuate potassium loss caused by thiazide diuretics and increase serum potassium when used alone If concomitant therapy of ACCUPRIL with potassium-sparing diuretics (eg, spironolactone, triamterene, or amiloride), potassium supplements, or potassium-containing salt substitutes is indicated, they should be used with caution along with appropriate monitoring of serum potassium (see PRECAUTIONS)

Tetracycline and other drugs that interact with magnesium: Simultaneous administration of tetracycline with ACCUPRIL reduced the absorption of tetracycline by approximately 28% to 37%, possibly due to the high magnesium content in ACCUPRIL tablets This interaction should be considered if coprescribing ACCUPRIL and tetracycline or other drugs that interact with magnesium

Lithium: Increased serum lithium levels and symptoms of lithium toxicity have been reported in patients receiving concomitant lithium and ACE inhibitor therapy These drugs should be co-administered with caution, and frequent monitoring of serum lithium levels is recommended If a diuretic is also used, it may increase the risk of lithium toxicity

Other agents: Drug interaction studies of ACCUPRIL with other agents showed

- Multiple dose therapy with propranolol or cimetidine has no effect on the pharmacokinetics of single doses of ACCUPRIL.
- The anticoagulant effect of a single dose of warfarin (measured by prothrombin time) was not significantly changed by quinapril coadministration twice-daily.
- ACCUPRIL treatment did not affect the pharmacokinetics of digoxin
- No pharmacokinetic interaction was observed when single doses of ACCUPRIL and hydrochlorothiazide were administered concomitantly

Carcinogenesis, Mutagenesis, Impairment of Fertility

Quinapril hydrochloride was not carcinogenic in mice or rats when given in doses up to 75 or 100 mg/kg/day (50 to 60 times the maximum human daily dose, respectively, on a mg/kg basis and 3 8 to 10 times the maximum human daily dose when based on a mg/m^2 basis) for 104 weeks Female rats given the highest dose level had an increased incidence of mesenteric lymph node hemangiomas and skin/subcutaneous lipomas Neither quinapril nor quinaprilat were mutagenic in the Ames bacterial assay with or without metabolic activation Quinapril was also negative in the following genetic toxicology studies *in vitro* mammalian cell point mutation, sister chromatid exchange in cultured mammalian cells, micronucleus test with mice, *in vitro chromosome* aberration with V79 cultured lung cells, and in an *in vivo* cytogenetic study with rat bone marrow There were no adverse effects on fertility or reproduction in rats at doses up to 100 mg/kg/day (60 and 10 times the maximum daily human dose when based on mg/kg and mg/m^2, respectively)

Pregnancy

Pregnancy Categories C (first trimester) and D (second and third trimesters): See WARNINGS, Fetal/Neonatal Morbidity and Mortality

Nursing Mothers

It is not known if quinapril or its metabolites are secreted in human milk Quinapril is secreted to a limited extent, however, in milk of lactating rats (5% or less of the plasma drug concentration was found in rat milk) Because many drugs are secreted in human milk, caution should be exercised when ACCUPRIL is given to a nursing mother

Geriatric Use

Elderly patients exhibited increased area under the plasma concentration time curve (AUC) and peak levels for quinaprilat compared to values observed in younger patients, this appeared to relate to decreased renal function rather than to age itself In controlled and uncontrolled studies of ACCUPRIL where 918 (21%) patients were 65 years and older, no overall differences in effectiveness or safety were observed between older and younger patients However, greater sensitivity of some older individual patients cannot be ruled out

Pediatric Use

The safety and effectiveness of ACCUPRIL in children have not been established

ADVERSE REACTIONS

ACCUPRIL has been evaluated for safety in 4960 subjects and patients Of these, 3203 patients, including 655 elderly patients, participated in controlled clinical trials ACCUPRIL has been evaluated for long-term safety in over 1400 patients treated for 1 year or more

Adverse experiences were usually mild and transient

Discontinuation of therapy because of adverse events was required in 4 7% of patients treated with ACCUPRIL in placebo-controlled hypertension trials

Adverse experiences probably or possibly related to therapy or of unknown relationship to therapy occurring in 1% or more of the 1563 patients in placebo-controlled hypertension trials who were treated with ACCUPRIL are shown below

Adverse Events in Placebo-Controlled Trials

	ACCUPRIL (N = 1563) Incidence (Discontinuance)	Placebo (N = 579) Incidence (Discontinuance)
Headache	5 6 (0.7)	10 9 (0 7)
Dizziness	3 9 (0 8)	2 6 (0.2)
Fatigue	2 6 (0 3)	1 0
Coughing	2.0 (0 5)	0 0
Nausea/Vomiting	1 4 (0 3)	1 9 (0 2)
Abdominal Pain	1 0 (0 2)	0 7

See PRECAUTIONS, Cough

Clinical adverse experiences probably or possibly related, or of uncertain relationship to therapy, occurring in 0.5% to 1 0% (except as noted) of the patients treated with ACCUPRIL (with or without concomitant diuretic) in controlled or uncontrolled trials (N = 4397) and less frequent, clinically significant events seen in clinical trials or post-marketing experience (the rarer events are in italics) include (listed by body system)

General: back pain, malaise

Cardiovascular: palpitation, vasodilation, tachycardia, *heart failure, hyperkalemia, myocardial infarction, cerebrovascular accident, hypertensive crisis, angina pectoris, orthostatic hypotension, cardiac rhythm disturbances*

Gastrointestinal: dry mouth or throat, constipation, *gastrointestinal hemorrhage, pancreatitis, abnormal liver function tests*

Nervous/Psychiatric: somnolence, vertigo, syncope, *nervousness, depression*

Integumentary: increased sweating, pruritus, *exfoliative dermatitis, photosensitivity reaction*

Urogenital: *acute renal failure*

Other: amblyopia, pharyngitis, sinusitis, bronchitis, *agranulocytosis, thrombocytopenia*

Fetal/Neonatal Morbidity and Mortality

See WARNINGS, Fetal/Neonatal Morbidity and Mortality.

Angioedema: angioedema has been reported in patients receiving ACCUPRIL (0. 1%) Angioedema associated with laryngeal edema may be fatal If angioedema of the face, extremities, lips, tongue, glottis, and/or larynx occurs, treatment with ACCUPRIL should be discontinued and appropriate therapy instituted immediately (See WARNINGS)

Clinical Laboratory Test Findings

Hematology: (See WARNINGS)

Hyperkalemia: (See PRECAUTIONS)

Creatinine and blood urea nitrogen: Increases (T1 25 times the upper limit of normal) in serum creatinine and blood urea nitrogen were observed in 2% and 2%, respectively, of patients treated with ACCUPRIL alone Increases are more likely to occur in patients receiving concomitant diuretic therapy than in those on ACCUPRIL alone These increases often remit on continued therapy

*In some patients, the antihypertensive effect may diminish toward the end of the once-daily dosing interval In such patients, an increase in dosage or twice-daily administration may be warranted

PD-103-MI-7457-C1(052)

PARKE-DAVIS
A Warner-Lambert Company
Morris Plains, New Jersey 07950

Colorectal Carcinoma in Rhode Island: Clinical Experience with 841 Cases

Clarence H. Soderberg, Jr, MD
J. Robert Bowen, MD
Brian A. Dorman, MD
John C. Pezzullo, PhD
Thomas K. Shahinian, MD
William R. Thompson, MD

Cancer mortality is approximately 10% higher in Rhode Island than the United States as a whole even when differences in age, gender, and race have been controlled.

In Rhode Island, colorectal cancer ranks first on the basis of newly diagnosed cancer cases and second only to lung cancer on the basis of deaths.[1] Our clinical experience with this common malignancy is reviewed here, not only to evaluate our performance and results, but to identify any features that might be characteristic of this highly urbanized state.

Material and Methods

The study group consisted of 841 operative cases of colorectal carcinoma, 425 males and 416 females. All patients had invasive carcinoma requiring surgery, other than biopsy alone, performed by five members of the Second Surgical Service at the Rhode Island Hospital, an affiliate of Brown University Medical School. Operations were performed between November 28, 1961, and December 29, 1987.

The segment of involved bowel was as presented in Table 1. The percentage of cecum, ascending, and transverse colon patients remained the same before and after 1975, 31%. The percentage of cecum and ascending colon patients alone was 18% before 1975 and 23% thereafter.

The records were reviewed retrospectively, and the data were entered into a microcomputer database for subsequent analysis. Presentation, type of surgery performed, extent of disease, complications, patterns of recurrence, and end-results are presented. Survival probability was estimated by the method of Kaplan and Meier.[2]

The age of the patient at the time of presentation was recorded as outlined in Figure 1. Ninety-six percent were over the age of 50 and 21% were over 80. It occurred most commonly in the eighth decade of life.

Presentation

The first presenting sign or symptom was bleeding for both rectal and sigmoid lesions closely followed by change in bowel habits. Descending colon and transverse colon patients most commonly presented with obstruction. Cecum/ascending colon patients were discovered most frequently with anemia. The five most common means of presentation in order of decreasing frequency were bleeding (255), change in bowel habits (173), anemia (109), obstruction (91), and abdominal pain (69). Figure 2 shows the percentage of the total number of colorectal patients who presented with each feature. When the carcinoembryonic antigen (CEA) was recorded preoperatively it was elevated 28% of the time.

ABBREVIATIONS USED:

CEA: Carcinoembryonic antigen

Clarence H. Soderberg, Jr, MD, is Clinical Associate Professor of Surgery, Brown University, Providence, Rhode Island and Chief, Second Surgical Service, Rhode Island Hospital, Providence, Rhode Island.

J. Robert Bowen, MD, is Clinical Associate Professor of Surgery, Brown University, Providence, Rhode Island and Surgeon, Second Surgical Service, Rhode Island Hospital, Providence, Rhode Island.

Brian A. Dorman, MD, is Clinical Assistant Professor of Surgery, Brown University, Providence, Rhode Island and Surgeon, Second Surgical Service, Rhode Island Hospital, Providence, Rhode Island.

John C. Pezzullo, PhD, is Director, Information Technology Center, Rhode Island Hospital, Providence, Rhode Island.

Thomas K. Shahinian, MD, is Clinical Assistant Professor of Surgery, Brown University, Providence, Rhode Island and Chief, Section of Surgical Endoscopy, Rhode Island Hospital, Providence, Rhode Island.

William R. Thompson, MD, is Clinical Professor of Surgery, Brown University, Providence, Rhode Island and Chief of Surgery, Rhode Island Hospital, Providence, Rhode Island.

Operations

Standard operative procedures were used including 100 abdominoperineal resections, 154 anterior resections of the rectum, 191 right colectomies, 26 extended right colectomies, and 275 colectomies. There were 23 local resections including transanal and parasacral approaches. Total abdominal colectomy was performed seven times. A liver resection was added to the main procedure five times. Anastomoses were recorded as being stapled 245 times and handsewn 493 times. Surgery was felt to be curative in 683 cases and palliative in 158.

Operative Findings

A modified Astler Coller classification (Table 2) was used to record the extent of disease at the time of initial surgery and the percent of each stage is listed for the five segments of the colorectum (Table 3). The fewer the early lesions (A,B_1) the greater the distance the tumor was from the anus. Synchronous lesions, only 10 in number, did not have distant spread.

Liver metastases were present in 124 cases (15%). In 20 (16%) of those having metastases the lesion was grossly solitary. When carcinoembryonic antigen levels were determined postoperatively they were elevated 23% of the time.

Other Therapy

Adjuvant chemotherapy was used in only 12 cases (1%). Adjuvant radiation therapy was delivered to 43 patients (5%).

Chemotherapy also was used infrequently for later recurrences (an additional 5% of cases). An additional 32 patients received infusional chemotherapy.

Complications

Complications were recorded in 257 cases (31%). Wound infection was the most common complication occurring in 51 patients (6%). The second most common cause of morbidity was postoperative paralytic ileus, which occurred in 44 patients (5%). Urinary tract complications were the next most common with 19 instances of urinary retention and 19 instances of urinary tract infection (4.5%). Pneumonitis occurred in 14 patients (2%). There were only seven instances (less than 1%) of pulmonary emboli recorded and six other patients developed phlebitis. There were 19 instances of clinically evident anastomotic leak (2%). There were five instances of wound dehiscence. Significant arrhythmias occurred in 12 patients (1%), congestive failure in nine, and documented myocardial infarction in five. Renal failure occurred in six patients. Nine patients experienced a cerebrovascu-

Table 1. **Colorectal Carcinoma (841 Cases)**

Segment of Involved Bowel	Number	Percent
Rectum	274	34
Sigmoid	233	28
Descending Colon	64	8
Transverse Colon	79	9
Ascending Colon/Cecum	181	22
Multiple Areas	10	1

Figure 1. **Age Distribution**

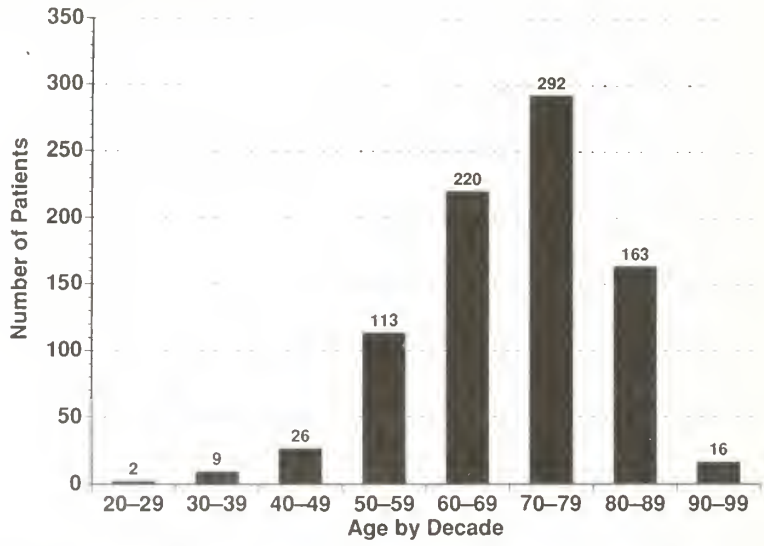
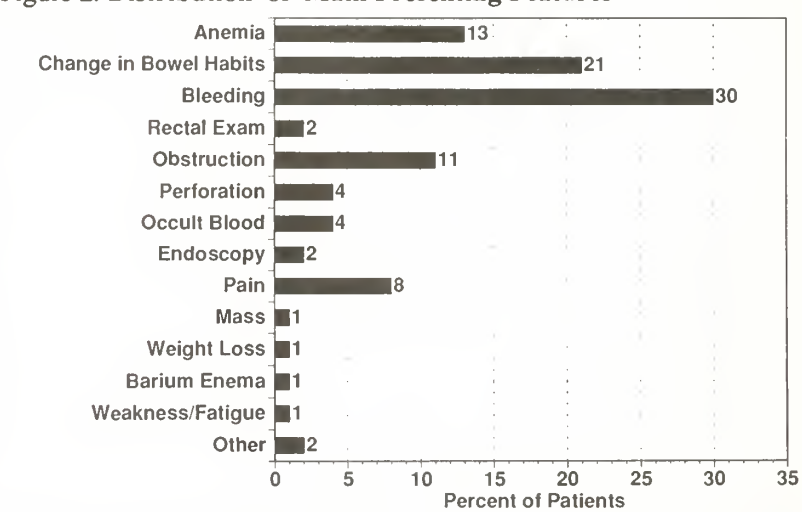


Figure 2. **Distribution of Main Presenting Features**



lar accident (1%). There was an in-hospital, or, if discharged, less than 30-day mortality rate of 3.2%.

Recurrences

The first area of recurrence was the liver in 83 patients (10%). The next most common area of recurrence was local in 78 patients (9%). Suture line recurrence was third and was recorded in 20 patients (2.4%). The next most common areas of first recurrence were regional nodes (11), lung (10), and bone (7). Secondary areas of recurrence were also most commonly liver (34), lung (31), local (27) and regional nodes (27).

The percentage of patients developing the two most common areas of recurrence following resection for cure are depicted in Table 4 for each site of origin. Local recurrences were more common following rectal carcinomas while the percentage of patients developing liver metastases remained approximately the same for all sites.

Survival

Survival rates for each segment of the colorectum are illustrated in Table 5. Five-year survival rates are slightly less than 50 percent in all sites. The survival for all areas are surprisingly similar and the survival curves for rectum compared to colon sites are essentially the same (Figure 3). The overall survival curve is shown in Figure 4.

Table 2. **Modified Astler Coller Staging**

Stage	
A	Superficial to Muscular Propria
B	Invasion into Muscular Propria
B_2	Invasion Through Entire Wall
B_3	Involvement of Adjacent Organs
C_1	Confined to Wall with Positive Nodes
C_2	Invasion through Entire Wall with Positive Nodes
C_3	Involvement of Adjacent Organs with Positive Nodes
D	Distant Spread

Table 3. **Extent of Disease at Surgery**

Stage	Rectum	Sigmoid	Descending	Transverse	Cecum/ Ascending	Multiple Sites
A	11%	12%	6%	1%	3%	10%
B_1	24%	11%	11%	10%	10%	10%
B_2	26%	33%	44%	43%	39%	30%
B_3	<1%	<1%	0%	6%	1%	0%
C_1	3%	2%	5%	1%	6%	10%
C_2	21%	21%	17%	20%	22%	30%
C_3	1%	1%	0%	1%	2%	10%
D	15%	20%	17%	16%	18%	0%

Table 4. **Recurrence Following Resection for Cure (%)**

	Local	Liver Metastases
Rectum	18	14
Sigmoid	10	15
Descending	11	13
Transverse	10	16
Ascending/Cecum	9	12

Discussion

Cancer mortality is about 10% higher in Rhode Island than the United States as a whole even when controlling for differences in age, gender, and race.[3] In our study of colorectal cancer, few cases were discovered by screening methods. Testing the stool for occult blood led to the diagnosis in 4% of the cases and routine endoscopy led to the discovery in only 2%. A delay in diagnosis until more serious signs or symptoms appear could lead to a higher mortality. In our series, surgery was only palliative in almost one-fifth of the patients. Seventy-seven percent of patients were Stage B_2 (invasion through the entire wall) or worse. The small size of Rhode Island and its urban nature would seem to make it an ideal place to perform and test screening methods that, to date, appear overdue.

Since 96% of the patients in this series were over the age of 50, this is probably the age where investigation for colorectal cancer should begin. Thirty-five percent of patients were between 70 and 79 years of age. Should everyone who reaches 70 years of age have a colonoscopy?

Adjuvant chemotherapy recently has been shown to be of benefit in the treatment of colorectal cancer patients.[4,5] Its use in the present series, which ended in 1987, was therefore understandably low (1%). Radiotherapy was perhaps also underutilized in this series in view of the recent National Institutes of Health Consensus Development Conference conclusion that in rectal cancer the best current adjuvant therapy included both chemotherapy and radiotherapy.[6]

The postoperative surgical mortality rate appears sufficiently low (3.2%), somewhat higher than that of the nearby Lahey Clinic (2%),[7] but significantly lower than a report from Rome, Italy (7%).[8] This mortality rate was achieved in spite of the fact that slightly more than one-fifth of the patients were 80 years or older.

Liver metastases and local recurrences are the most frequent site of failure and emphasize the need for both systemic and local adjuvant

therapy. Overall survival in this series remains as it has been for several decades.

It was surprising to note that in our patients those with rectal carcinoma did not appear to have a worse prognosis. The survival curves of rectal carcinoma compared to the remaining colon (Figure 3) appear identical. This suggests that the biology of the tumors might not be different and that previous survival differences were related to the method of treatment – abdominoperineal resection vs bowel resection with anastomosis. It seems likely that the increasing use of sphincter-saving operations for rectal carcinoma might decrease the high incidence of local recurrence seen in that area.

References

1. First Annual Report Rhode Island Cancer Registry. *Cancer*. RI, 1987.
2. Kaplan EL, Meier P. Nonparametric estimation from incomplete observations. *J Am Stat Assoc* 53:457-481, 1958.
3. Scott HD, Fulton JP, Korniske M. Cancer control in Rhode Island: Blueprint for the 1990s. *RI Med J* 73:591-597, 1990.
4. Wolmark N, Fisher B, Rochette H, et al. Postoperative adjuvant chemotherapy or BCG for colon cancer: Results from NSAPB protocol CO_1. *J Natl Cancer Inst* 80:30-36, 1986.
5. Laurie JA, Moertel CG, Fleming TR, et al. Surgical adjuvant therapy of large-bowel carcinoma; an evaluation of levamisole and the combination of levamisole and fluorouracil. *J Clin Oncol* 7:1447-1456, 1989.
6. National Institutes of Health: Consensus Development Conference Statement, pp. 16-18, April 1990.
7. deLeon ML, Schoetz DJ, Coller JA, Veidenheimer MC. Colorectal cancer: Lahey Clinic experience, 1972-1976: An analysis of prognostic indicators. *Dis Colon Rectum* 30:237-242, 1987.
8. Pescatori C, Mattana Maria G, Ferrara A, Lucibello L. Outcome of colorectal cancer. *Br J Surg* 74:370-372, 1987.

Address correspondence to:
Clarence H. Soderberg, Jr., MD
235 Plain Street
Providence, RI 02905

Table 5. **Percent Survival**

Site	Percent Survival 42 Months	Survival 60 Months
Rectum	62	47
Sigmoid	58	45
Descending	57	47
Transverse	59	48
Ascending/Cecum	57	46

Figure 3. **Kaplan and Meier Survival Curves for Colon and Rectal Carcinoma**

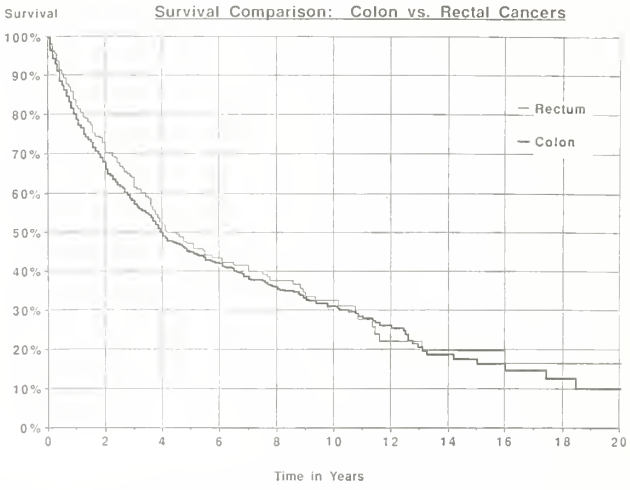
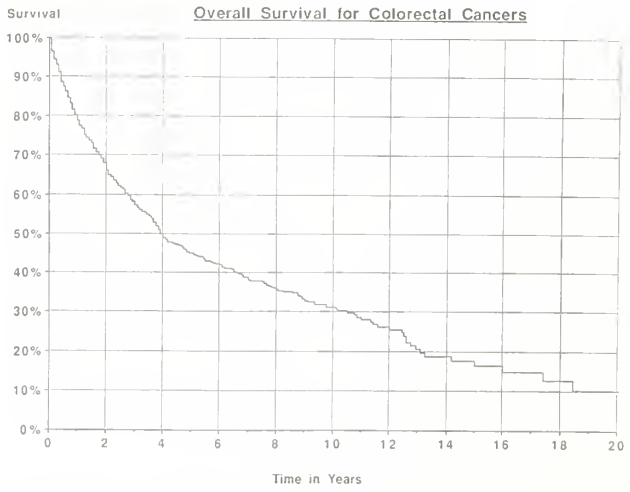
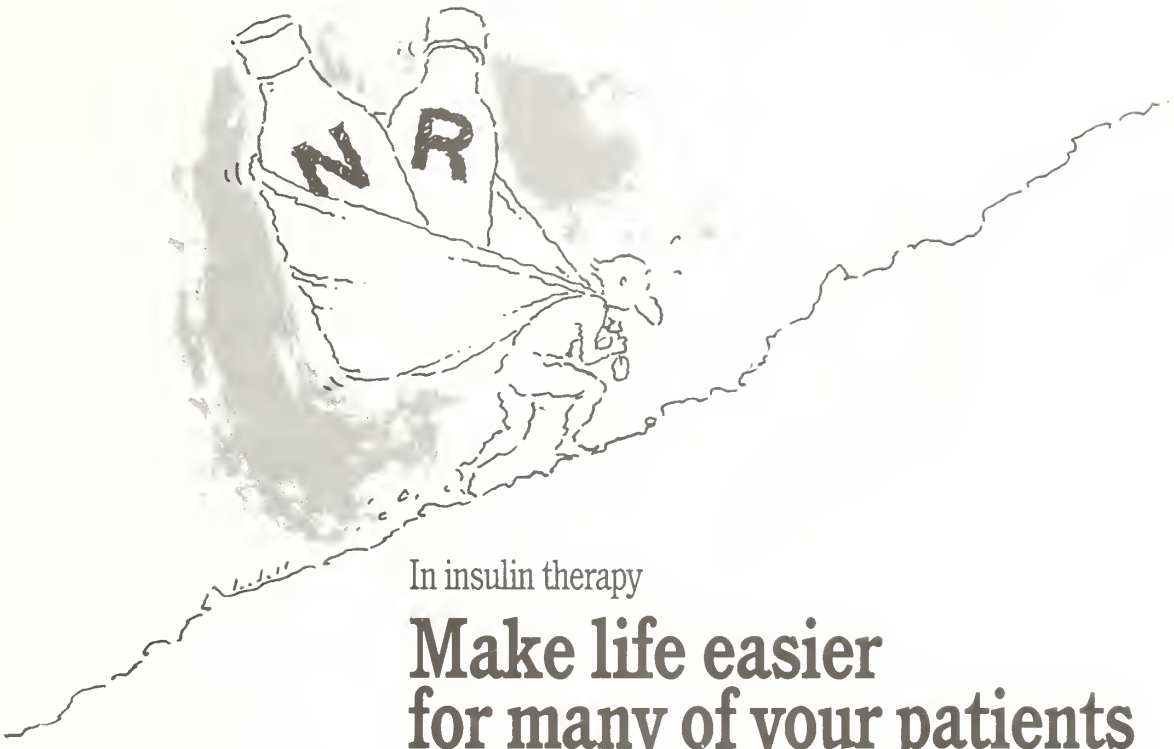


Figure 4. **Kaplan and Meier Survival Curves for Entire Series of Colorectal Carcinoma**





In insulin therapy

Make life easier for many of your patients

Humulin 70/30. Convenient and simple to administer. No more mixing. No more mixing errors. All of which makes living with diabetes a little easier for patients. And compliance a lot easier to achieve.

Humulin® 70/30

70% human insulin isophane suspension
30% human insulin injection
(recombinant DNA origin)

The patient-friendly premix

Global Excellence in Diabetes Care

Eli Lilly and Company
Indianapolis, Indiana
46285

WARNING: Any change of insulin should be made cautiously and only under medical supervision.

HI-7905-B-249327 ©1992, ELI LILLY AND COMPANY

PHYSICIAN OFFICE SUPPLY COMPANY
ESCO DRUG CO., INC.

110 Lockwood Street
Providence, Rhode Island

Mark S. Goldberg, R.Ph., B.S., M.B.A., C.F.
Pharmacy Manager
421-3250
FAX 621-9889

- vaccines
- injectables
- chemotherapeutics
- paper products
- surgical dressings
- low protein products
- specialty compounding: progesterone suppositories
- certified orthotic fitter
- Jobst, Vairox, Warm and Forms
- RI Leading Diabetic Supplier

*** BEST PRICES AROUND ***

CALL FOR A PRICE QUOTE

STORE HOURS
Monday thru Friday 8:00 AM to 6:00 PM
Saturday 9:00 AM to 1:00 PM

Special Orders Gladly Accepted

Carpal Tunnel Syndrome: A Review

Arnold-Peter C. Weiss, MD
Edward Akelman, MD

Carpal tunnel syndrome involves classic symptoms of numbness and paresthesias in the radial three and one-half digits, most frequently nocturnal, and pain associated with this distribution.

Carpal tunnel syndrome (CTS), or entrapment of the median nerve at the wrist, well described in the medical literature, plays an ever-increasing role in medical practice. In 1854, Sir James Paget described the first case of an enlarged median nerve at the entrance of the carpal canal with associated adhesions in a patient who underwent arm amputation for intractable pain and sensory dysfunction after a distal radius fracture.[1] Several sporadic descriptions of median nerve entrapment followed during the next century.[2] However, carpal tunnel syndrome as a defined clinical entity first was described by Phalen in a series of publications in the 1950s, 1960s and 1970s.[3,4] Despite improved dissemination of knowledge regarding carpal tunnel syndrome, the incidence of this condition seen in medical practice appears only to have increased with time.

Anatomy

The carpal tunnel is a narrow channel formed by the transverse carpal ligament anteriorly, the hook of hamate ulnarly, the trapezium radially, and the dorsal carpus. All of the flexor tendons travel through this space, as does the median nerve. Any increase in the size of the contents of this canal, decrease in the size of the canal proper, or increase in the intrinsic pressure within the carpal tunnel may cause median nerve compression.

Patient History and Symptoms

Carpal tunnel syndrome is the single most common compressive neuropathy. Entrapment of the median nerve, most frequently at the wrist, presents with altered sensory changes in the radial 3-1/2 digits and pain or burning in the hand and wrist. Less frequently, patients may be noted to have motor thenar muscle weakness and autonomic dysfunction as well as numbness in the median nerve distribution. These patients more commonly are associated with chronic carpal tunnel syndrome.

Transient numbness and paresthesias of the thumb, index, middle, and radial half of the ring fingers are some of the earliest findings of median nerve compression. Frequently, not all digits are involved and only one or two may appear consistently symptomatic. Patients who complain of constant sensory changes not relieved by limiting activities or postural changes of the wrist are often in an advanced state of median nerve entrapment. It is common to find patients complaining of these symptoms most frequently occurring at night. Exacerbation of symptoms noted during daytime hours has been associated with repetitive motion activities at work or in the home.

The second hallmark finding is that of pain in the involved hand and wrist with frequent radiation into the forearm and upper arm, occasionally even including the neck region. The pain most frequently occurs nocturnally and may be relieved by "shaking" the hand. A position of flexion in the wrist tends to exacerbate the symptoms in most patients.

In general, a careful history most frequently will eliminate other causes of sensory dysesthesias or pain in the hand. The history should include the patient's normal daily extremity activities and a work history. Several medical conditions have been associated with carpal tunnel syndrome. Patients with connective tissue diseases such as rheumatoid arthritis, neuropathic conditions such as diabetes mellitus, and alterations of fluid imbalance such as occurs in pregnancy frequently can experience changes in median nerve sensibility.[6]

Physical Examination and Electrophysiologic Testing

Physical examination is used to confirm localized median nerve compression at the wrist and to evaluate the extent of denervation present. Two

ABBREVIATIONS USED:

CTS: Carpal tunnel syndrome
EMG: Electromyography
NCV: Nerve conduction velocity

Arnold-Peter C. Weiss, MD, is Assistant Professor, Department of Orthopedics, Brown University, and Rhode Island Hospital, Providence, Rhode Island.

Edward Akelman, MD, is Assistant Professor, Department of Orthopedics, Brown University, and Rhode Island Hospital, Providence, Rhode Island.

physical examination tests remain the standard of evaluating carpal tunnel syndrome. The wrist flexion test as initially described by Phalen is probably the most sensitive test for carpal tunnel syndrome.[3] In this examination, the wrist is flexed as much as possible and held in this position for up to 60 seconds (Figure 1). The reproduction of numbness or paresthesias at the distal fingertips in the median nerve distribution defines a positive test. Local percussion sensitivity over the median nerve at the carpal tunnel, most frequently called a Tinel's sign,[5] is another valuable diagnostic test for carpal tunnel syndrome (Figure 2). Other helpful, but less sensitive diagnostic tests involve local compression of the median nerve at the carpal tunnel with reproduction of symptoms distally, the evaluation of moving two-point discrimination alterations, and changes in light touch sensibility. The abductor pollicis brevis and opponent pollicis should be examined. Evident thenar muscle atrophy and weakness denotes advanced nerve compression. Careful examination of other related areas such as the cervical spine, shoulder, elbow and pronator muscle mass must be evaluated as causes of more proximal nerve compression.

The use of nerve conduction velocity and electromyographic studies have been advocated frequently in aiding the diagnosis of carpal tunnel syndrome. These tests are most useful in patients who may have an overriding polyneuropathy complicating the picture of whether nerve compression is actually present. These electrophysiologic tests are also useful in patients whose histories and physical examinations are atypical and may help to stage the degree of compression in the disease, aiding in treatment decision-planning. Although these tests provide important adjunctive help in the diagnosis of carpal tunnel syndrome, they are not as sensitive as a patient with a classical history and physical examination. A false-negative rate of 10% for electrophysiologic testing has been noted with a success rate following surgical decompression in this group being comparable to that in a group of patients who have an electrically documented median nerve deficit.[7]

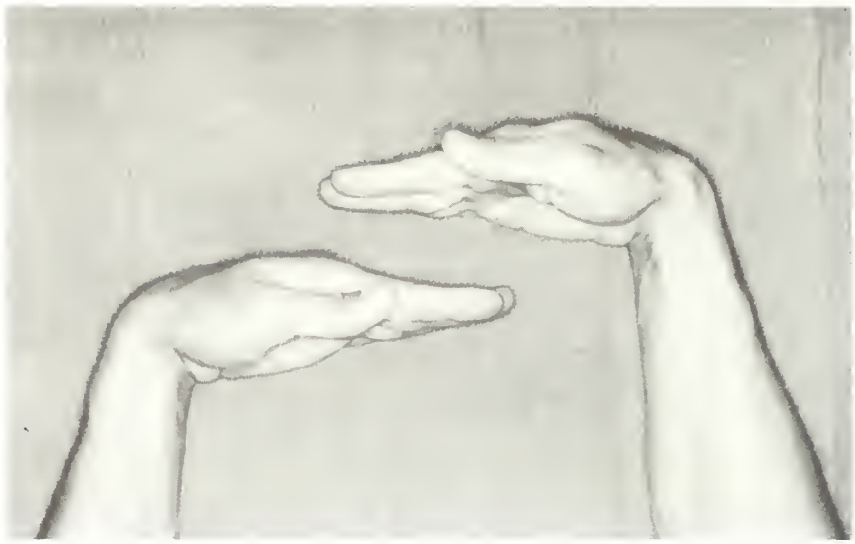


Fig. 1–Maximal flexion of the wrist may reproduce symptoms of carpal tunnel syndrome.

Radiographic and Laboratory Studies

Occasionally other types of patient evaluation are necessary in the management of CTS. Patients with a prior history of wrist trauma or older patients with osteoarthritis may need radiologic evaluations. Routine carpal tunnel X-rays are rarely of use.

Patients with a history of systemic illness or multiple extremity or joint involvement may need laboratory tests such as an erythrocyte sedimentation rate, fasting blood glucose, rheumatoid factor or anti-nuclear antibody study. These tests are not necessary for routine cases of carpal tunnel syndrome.

Fig. 2–Local percussion sensitivity of the median nerve is frequently seen in patients with carpal tunnel syndrome.

Conservative Treatment

The mainstays of conservative therapy for carpal tunnel syndrome remain the modification of extremity usage, the use of a neutral wrist splint, and the injection of corticosteroid medication into the carpal canal. Nonsteroidal anti-inflammatories have not been shown to be statistically effective in the treatment of carpal tunnel syndrome. In the absence of thenar motor weakness or atrophy and in patients with symptoms of less than one year's duration, a combination of wrist neutral splints and steroid injections has been found to be most useful.[8] However, in this group treated with a single steroid injection and a three-week period of wrist splinting, only 22 percent of all patients remained symptom-free at an average 18-month follow-up. The likelihood of success decreases further if the patient is involved in work requiring heavy manual

repetitive motion and high demand hand and wrist activities. Nonoperative treatment without any resolution of symptoms within six weeks generally can be considered a failure of conservative treatment. Many of these patients present with severe median neuropathy with denervation present at the initial evaluation and have significant muscle fibrillations noted on electromyographic studies. In these patients, surgical decompression of the median nerve at the carpal canal is warranted. In patients who have partial relief of symptoms from the splinting/steroid injection therapy, an additional one to two months of conservative treatment is useful to see whether symptoms completely resolve. Patients left with residual complaints after a three-month period should undergo surgical decompression of the carpal canal.

Fig. 3–The 2.5 to 3.0 cm incision used in open transection of the transverse carpal ligament. Excellent visualization during the entire procedure can be accomplished through this limited approach with appropriate retraction.

Operative Treatment

Two surgical approaches currently are available to release the transverse carpal ligament. An open procedure, using a limited curvilinear or longitudinal incision between the thenar and hypothenar eminences of approximately 3 cm in length without extension proximal to the wrist volar flexion crease is most commonly performed (Figure 3). Using this technique, the entire transverse carpal ligament can be transected under direct vision.

Following this release, the volume of the carpal tunnel increases, primarily in an anterior-posterior direction, allowing symptomatic relief after surgery.

A second technique used is that of endoscopic release of the transverse carpal ligament.[9] This technique uses an incision just proximal to the volar wrist flexion crease of about 1 cm in width and a second incision at the mid-region of the palm (Figure 4). Under direct endoscopic vision, the transverse carpal ligament is transected using a set of three individual, differently designed knives (Figure 5).

Both techniques appear to have advantages and disadvantages. Although open carpal tunnel release is extremely predictable in relieving patients' symptoms and has an extremely low complication rate due to the ability to easily visualize structures prior to being transected, persistent palmar tenderness for several months does remain a hallmark of this technique.

The endoscopic carpal tunnel release technique appears, in a preliminary study, to decrease palmar tenderness postoperatively and may allow an earlier return to work for specific patients (non-workers' compensation).[10] Balanced by this advantage is the higher risk of transecting the superficial palmar arterial arch, adjacent flexor tendons, or digital nerves because of lessened visualization of the transverse carpal ligament. Even a case of complete median nerve transection has been seen. With improved visualization equipment and surgeon familiarity with the techniques involved in endoscopic carpal tunnel release, these drawbacks may be minimized.

Currently, several prospective randomized studies examining open vs endoscopic carpal tunnel release are being undertaken to delineate clearly return of grip and pinch strength, time to return to work, post-operative palmar tenderness, and risk of damage to adjacent structures. The final outcome of the risks and benefits associated with endoscopic carpal release must be measured by these carefully controlled studies to document whether improved overall outcome is seen in patients requiring carpal tunnel release.

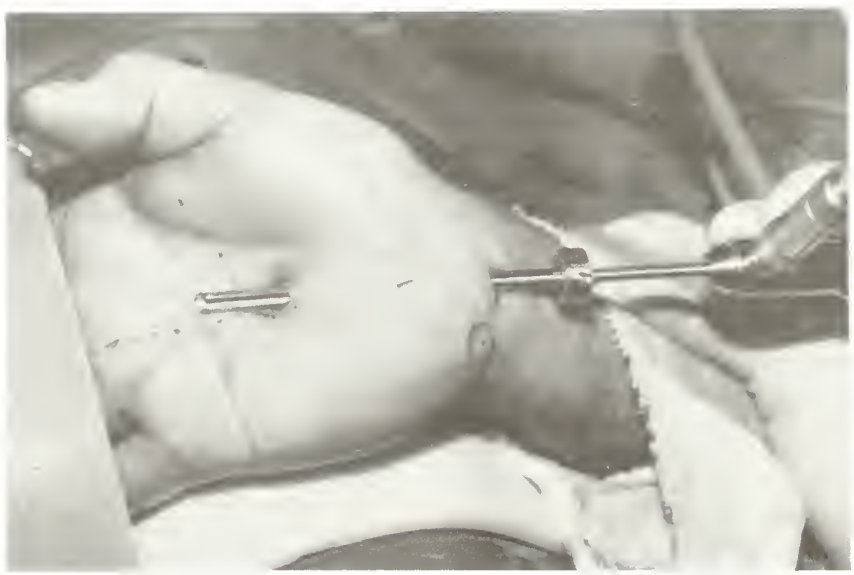


Fig. 4–Endoscopic release of the transverse carpal ligament using the two portal system.

Summary

Carpal tunnel syndrome involves classic symptoms of numbness and paresthesias in the radial 3-1/2 digits, most frequently nocturnal, and pain associated with this distribution. Thenar weakness and autonomic dysfunction rarely are seen in this syndrome except in advanced cases. Provocative tests on physical examination such as the wrist flexion test and the local percussion sensitivity test over the median nerve can be extremely helpful in determining and confirming the diagnosis. Nerve conduction velocity and electromyographic studies of the median nerve and its compression can be helpful especially in difficult cases involving a complex differential diagnosis. It has been clearly documented that a negative NCV/EMG study by itself, does not exclude the possibility of carpal tunnel syndrome. The hallmark of the diagnosis remains the history and a careful physical examination.

Treatment initially consisting of wrist splint immobilization and steroid injection into the carpal canal can provide initial relief and elimination of symptoms on a long-term basis in several patient groups. Patients without any resolution of symptoms after two to three months of conservative treatment or those with symptoms of greater than one year's duration generally can be considered candidates for surgical decompression of the carpal canal. The likelihood of operative treatment being required for resolution of symptoms is heightened if the patient is involved in daily manual repetitive activities of the hand and/or wrist. Surgical decompression can be accomplished by either a limited open technique or the new endoscopic released technique. Currently advantages and disadvantages are present for both procedures, and careful, controlled studies in a prospective and randomized fashion will be required to further delineate the indications for either procedure. Nevertheless, carpal tunnel release remains one of the operative procedures with the most predictable outcome in relief of symptoms for the patient.

Fig. 5–Visualization of a knife cut through the endoscope. The endoscope does not allow concurrent circumferential visualization of the carpal tunnel.

References

1. Paget J. *Lectures on Surgical Pathology* 1st ed. Philadelphia: Lindsey and Blakiston, 1854.
2. Learmonth J. The principles of decompression in the treatment of certain diseases of peripheral nerves. *Surg Clin North Am* 13:905, 1933.
3. Phalen G. Reflections on 21 years ' experience with the carpal tunnel syndrome. *JAMA* 212:1365, 1970.
4. Phalen G, Gardner W, Lalonde A. Neuropathy of the median nerve due to compression beneath the transverse carpal ligament. *J Bone Joint Surg* 32A:109, 1950.
5. Tinel J. Le signe du 'fourmillement' dans les lesions des nerfs peripheriques. *Presse Med* 23:388, 1915.
6. Grokoest A, DeMartini F. Systemic disease and the carpal tunnel syndrome. *JAMA* 155:635, 1954.
7. Grundberg A. Carpal tunnel decompression in spite of normal electromyography. *J Hand Surg* 8:348, 1983.
8. Gelberman R, Aronson D, Weisman M. Carpal tunnel syndrome: results of a prospective trial of steroid injection and splinting. *J Bone Joint Surg* 62A:1181, 1980.
9. Chow J. Endoscopic release of the carpal ligament a new technique for carpal tunnel syndrome. *Arthroscopy* 5:19-24, 1989.
10. Agee JM, Tortosa R, Berry D, Peimer CA. Endoscopic Release of the carpal tunnel: a randomized prospective multicenter study. Transaction of the 45th American Society for the Surgery of the Hand; September 24, 1990; Toronto, Canada.

Address correspondence to:
Arnold-Peter C. Weiss, MD
Rhode Island Hospital
593 Eddy Street
Providence, RI 02903

July 1992
Contents

RHODE ISLAND
MEDICINE

Medical Education in Rhode Island

QUESTION:

WHAT ARE THE THREE MOST IMPORTANT THINGS TO CONSIDER WHEN CHOOSING AN INSURANCE AGENCY?

ANSWER:

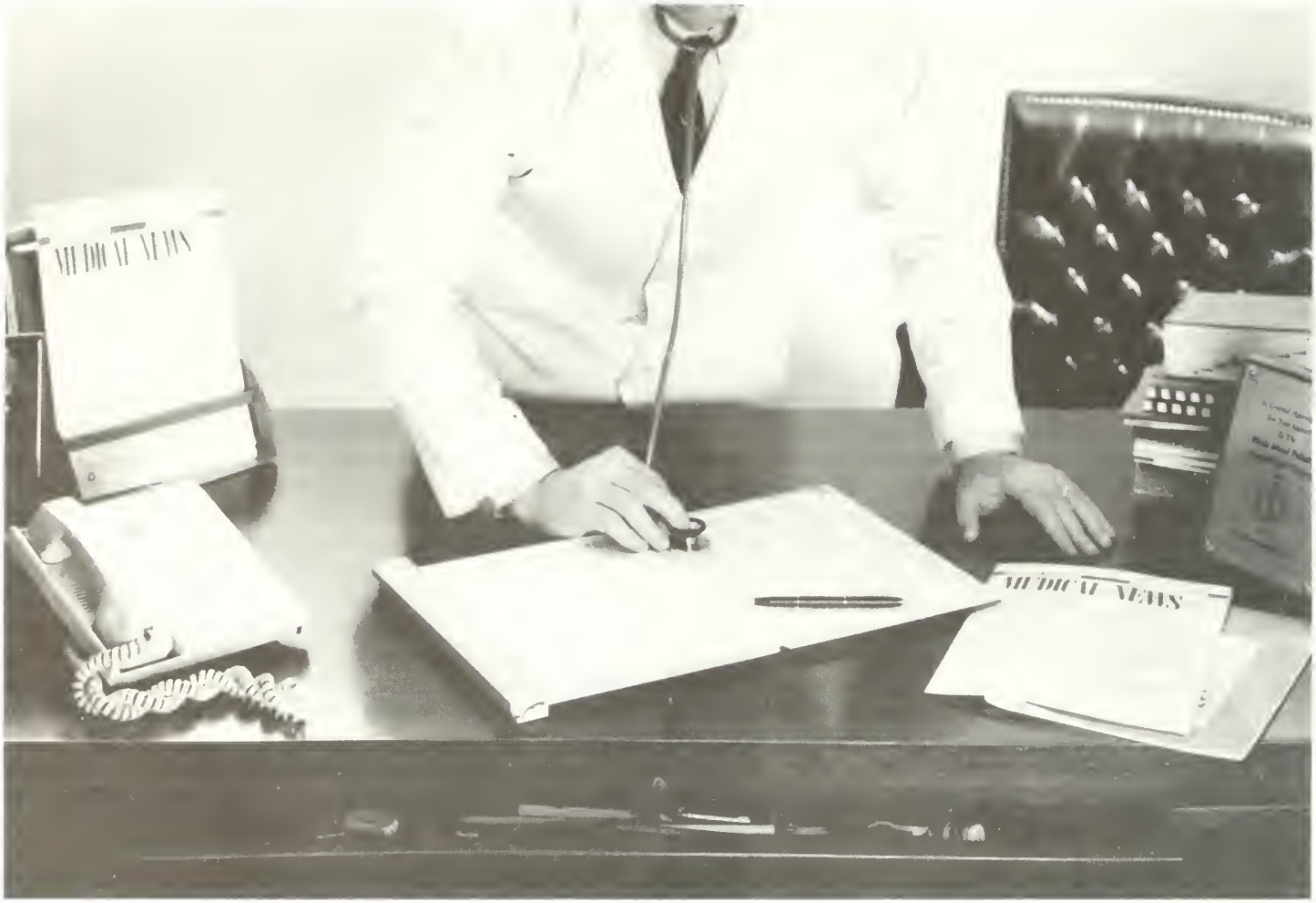
EXPERIENCE, EXPERIENCE, EXPERIENCE

INSURANCE SINCE 1879

STARKWEATHER & SHEPLEY INC. - (401) 421-6900

Morton Smith, Inc. - (401) 861-6800

155 South Main Street
Providence, Rhode Island 02903



IS YOUR FINANCIAL PROGNOSIS AS BRIGHT AS IT SHOULD BE?

RIMS Insurance Brokerage Corporation (IBC) introduces complete Life Insurance and Financial Planning services. Now, the firm that provides outstanding malpractice insurance programs and workers' compensation coverage, introduces life insurance and investment services designed specifically for the health care professional.

Insuring over one third of all licensed physicians in Rhode Island, IBC is known for quick and informed service. We have programs customized for all stages of a physician's practice — from the beginning practitioner to the practitioner nearing retirement.

And now — the IBC is your one-stop resource for a complete selection of life, health, disability and investment products. Take advantage of this new path to financial security and ensure that your long-term financial prognosis is every bit as bright as it should be. **For a free financial check-up, call IBC at 272-1050.**

RIMS Insurance Brokerage Corporation

One Hayes Street • Providence, Rhode Island 02908

Phone (401) 272-1050 • Fax (401) 272-1051 • RI Toll Free 800-559-6711

Immune Neutropenia and Pregnancy

Joseph R. Salvatore, MD
Alan Weitberg, MD

Immune neutropenia is a clinical entity characterized by neutropenia, positivity of one or more anti-neutrophil antibodies and a spectrum of bone marrow findings.

Neutropenia is a common medical problem with a number of well-recognized etiologies. Among the more common of these are: neutropenia induced by anti-neoplastic chemotherapeutic agents (which may be the most common etiology),[6] neutropenia induced by drugs other than chemotherapy agents, and hematologic disease including leukemia and myelodysplasia, alcoholism, and infection. This spectrum of neutropenia represents both increased destruction and decreased neutrophil production. Since mature neutrophils have a short life span in the peripheral blood of only 6 to 7 hours, any condition that induces decreased production or increased destruction of neutrophils will cause a rapid fall in total peripheral neutrophil counts.

The major consequence of decreasing neutrophil counts is susceptibility to infections, mostly from mucous membranes, skin, and normal intestinal flora. The incidence of severe infection increases dramatically with white blood cell counts of 500 or less.[7]

Immune neutropenia is a clinical entity characterized by neutropenia, positivity of one or more anti-neutrophil antibodies and a spectrum of bone marrow findings ranging from normal to selective hypoplasia of the neutrophil series.[1]

The exact mechanisms of this disease are unclear. Immune thrombocytopenia is a more common immune cytopenia with substantial literature and experience on the treatment of this disease, including during pregnancy.[2] It is important to note that although there is some experience in treating immune neutropenia in different situations, there appears to be little available data on the treatment of immune neutropenia during pregnancy and the effect of this treatment on pregnancy outcome.

We report a case of successful pregnancy outcome in an 18-year-old woman with immune neutropenia treated with intravenous immune globulin (Alpha Therapeutics) during the course of her pregnancy. A search of the medical literature revealed substantial experience in the treatment of immune thrombocytopenia during pregnancy but no reports of treatment of immune neutropenia during pregnancy.

Case Report

The young woman first came to medical attention because of a petit mal seizure when she was 10, in November 1981. Prior to admission for this seizure disorder she was found to have a leukopenia of 2300 with 5% poly-morphonuclear leukocytes, and 5% bands. According to the patient's personal physician, she had not been started on any medication prior to the hematologic determination. All other blood tests were negative. During this initial admission, she was worked up for the seizure disorder, treated with phenobarbitol and zarontin, and had a bone marrow aspirate and biopsy that showed iron-negative marrow with hypercellularity. In January 1982, the anti-seizure medication was changed to sodium valproate.

The patient was reevaluated at a referral center for both the seizure disorder and the leukopenia in April 1982. The findings at that time were: (1) confirmation of the neutropenia, (2) mild splenomegaly not thought to be contributing to the condition, and (3) positive anti-neutrophil antibodies, both IgG and C_3. This was diagnosed an idiopathic immune neutropenia. No specific therapy was recommended for the blood dyscrasia.

The patient was first evaluated by one of us (JRS) in February 1986 and found to have a total WBC of 1900.

ABBREVIATIONS USED:

ANA: Anti-nuclear antibodies
CBC: Complete blood count
IV: Intravenous
WBC: White blood cell count

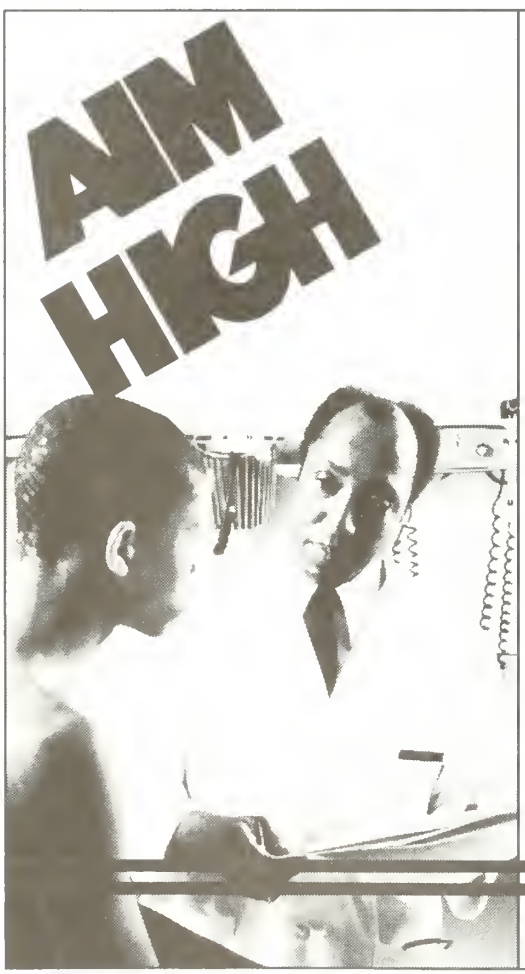
Joseph R. Salvatore, MD, is Chief, Division of Hematology/Oncology, Kent County Memorial Hospital, Warwick, Rhode Island, and Clinical Assistant Professor of Medicine, Brown University, Providence, Rhode Island.

Alan Weitberg, MD, is Director, Division of Medical Oncology, and Associate Professor of Medicine, Brown University, and Interim Chairman of Medicine for Clinical Services, Roger Williams Medical Center, Providence, Rhode Island.

Initial therapy consisted of monitoring CBCs, frequent examination, and treatment of infection when present. A bone marrow aspirate and biopsy done in May 1986 showed hypercellularity and absent iron stores. Additional studies done showed: (1) no splenomegaly or clinical evidence of collagen vascular disease; (2) ANA and rheumatoid factor negative, and (3) patient as taking no medications. In 1986, she required two admissions for infections (posterior pharyngitis with bilateral otitis media). During this time WBCs ranged from 1200 to 2700, with infection developing when the WBC was less than 1500. There were no admissions for infective processes in 1987, although the patient was admitted in August 1987 for an acute abdomen and was found to have, at laparotomy, a segment of colon and terminal ileum containing: "acute ulcerative transmural ulcerative colitis and ileitis." After the surgery, this problem required no further treatment and has not recurred. There were no admissions for infections in 1988, and WBCs ranged from 1500 to 2500.

After a series of infections of mucous membranes and skin abscesses in early 1989, she was started on prednisone from April to November 1989. The patient required dosages of 50 to 60 mg/day of prednisone to maintain a WBC of 2000, and when tapered to 5 to 10 mg/day, her WBC fell below 1500. The patient expressed a desire to be taken off prednisone, if possible, because the side effects at the aforementioned dosages were almost intolerable. Upon readmission in November 1989 for infection with a WBC of 800 while on 50 mg/day of prednisone, it was decided to begin weekly intravenous immune globulin (Alpha Therapeutics) at 24 grams each treatment. Between December 1989 and July 1990, WBCs ranged from 3500 to 5000, and she was without infection.

In July 1990, the patient was noted to be one month pregnant, and immune globulin was withheld. However, within a few weeks her WBC had fallen to 800, and she was admitted and started on immune globulin daily, again at 24 grams per treatment. She was discharged from the hospital with a WBC of 2700, and no detectable problems with the pregnancy. From August 1990 until delivery in March 1991, she was maintained on weekly immune globulin at 24 grams per dose, with WBCs of 4000 to 5000. A healthy baby boy was delivered in March 1991. Although the infant's WBC was initially lower, he recovered from this without incident. He required a hospitalization in May 1991 for a lower than expected WBC for his age. The infant is now being followed for "immune



CREATE A MEDICAL BREAKTHROUGH.

Become an Air Force physician and find the career breakthrough you've been looking for.

- No office overhead
- Dedicated, professional staff
- Quality lifestyle and benefits
- 30 days vacation with pay per year

Today's Air Force provides medical breakthroughs. Find out how to qualify as a physician or physician specialist. Call

USAF HEALTH PROFESSIONS
TOLL-FREE
1-800-423-USAF

AIR FORCE

neutropenia." Of relevance to this case is that the patient has a sister 5 years older, with immune neutropenia not requiring treatment and followed by one of us (JRS). She has delivered two children without problems, and neither child has hematologic disease. Other members of this patient's family have no hematologic disorders.

Discussion

We report the successful outcome of pregnancy in a patient with chronic immune neutropenia, treated with IV immune globulin during the pregnancy. The general pattern of this patient's disease appears consistent with that described by Logue, et al,[3] and our treatment experience is similar to that reported by Ventura, et al.[4] Although the medical literature showed ample data regarding the treatment of immune thrombocytopenia with IV immune globulin during pregnancy, we could find no similar report for chronic immune neutropenia. Despite at least one episode of the WBC falling below 1000 during the first trimester, there were no serious infections during the pregnancy, and no apparent ill effects to the newborn ascribable either to the immune neutropenia or the IV immune globulin. The fact that lower than expected WBCs have been discovered in the infant does not tell us if this is de novo disease or an immune problem passed on from the mother.

References

1 Williams WJ et al, eds. Neutrophil disorders: Benign quantitative of neutrophils. In *Hematology*. New York: McGraw-Hill, 1990.

2 Brussel JB. Intravenous immunoglobulin therapy of immune hematological disease. In Garner RJ and Sacher RA, eds., *Intravenous Gammaglobulin Therapy*. Arlington, VA: American Association of Blood Banks, 1988.

3 Logue GL. Idiopathic neutropenia: Autoneutrophil antibodies and clinical correlations. *Am J Med* 90:211-216, 1991.

4 Ventura A. Intravenous immunoglobulins in immune neutropenia. *Helvetica Poediatrica Acta* 41:495-500, 1987.

5 Mann K. Long-term remission of immune neutropenia and treatment with high-dose IV 75-immunoglobulin. *Klinische Wochenschift* 65:985-988, 1987.

6 Wilson JD, ed. Leukocytosis, leukopenia, eosinophilia In *Harrison's Principles of Internal Medicine*. New York: McGraw Hill; chap. 64, pp 361, 1991.

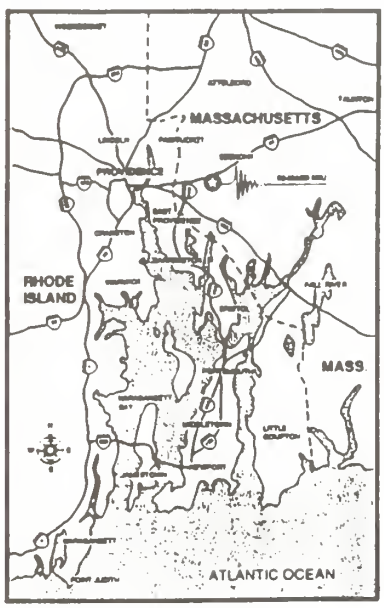
7 DeVita VT, Hellman S, Rosenberg SA, eds. Infections in the Cancer patient. In *Cancer: Principles and Practice of Oncology*. Philadelphia: JB Lippincott; chap. 59, 1989.

Address correspondence to:
Joseph R. Salvatore, MD
Kent County Memorial Hospital
455 Tollgate Road
Warwick, RI 02886

MAGNETIC RESONANCE IMAGING

RI-MASS MRI

309 Taunton Ave. (Rt 44), Seekonk, MA 02771



- Prompt Scheduling (within 24 hours)
- Pleasant Outpatient Setting
- High Quality Images (Sent to your office within 24 hours.)
- Latest Generation MRI Technology (3D and MR Angiography available)

RI-MASS MRI is a state of the art magnetic resonance imaging facility conveniently located on Taunton Avenue just blocks from the state line. To learn more about RI-MASS MRI or to receive more information about our facility (Rx pads, patient brochures, etc.) please contact Ruth Nash (Site Manager) at **1-800-848-9661.**

Patient Scheduling

1-(800)-848-9661

THE NEWLY APPROVED MEDICAL ASSOCIATION TRUSTS
(Summit Bancorporation, Trustee)
(CoreStates Bank, Trustee)

* V.E.B.A. PLAN

FEATURES

UNLIMITED TAX DEDUCTIBLE CONTRIBUTIONS

REGARDLESS OF YOUR PENSION SITUATION

AND IS NOW

IRS APPROVED FOR USE BY DOCTORS IN OTHER STATES

EVEN IF . . .

- YOUR PENSION PLAN IS OVER FUNDED
- YOUR PENSION PLAN IS MAXIMUM FUNDED
- YOU HAVE NO PENSION PLAN

PLEASE SEND ME A copy of the I.R.S. "Favorable Letter of Determination" and other relevant information on your *V.E.B.A. Plan

NAME _____

ADDRESS _____

DATE OF BIRTH _____ TELEPHONE # (____) _____

Mail to: THE KIRWAN COMPANIES
402 MIDDLETOWN BLVD., SUITE 202
LANGHORNE, PA 19047

(800) 969-7666 ..... (215) 750-7616 ..... FAX (215) 750-7791

*VOLUNTARY EMPLOYEE BENEFITS ASSOCIATION

Transfer from Animal to Human Insulin: A Clinical Experience

Charles B. Kahn, MD
R. Preston Lamberton, MD
Dennis S. Krauss, MD

Based on data from our charts, transfer to human insulin was accomplished without untoward problems.

Experimental use of human insulin of recombinant DNA origin (Humulin®, Lilly, Indianapolis, IN) was first reported in 1979, and it became commercially available in 1983. Semisynthetic human insulin (Novolin®, Novo Nordisk, Princeton, NJ) was developed in 1976, and clinical use began in 1983. These events appeared to herald a significant advance in the treatment of insulin dependent and insulin requiring diabetes mellitus, and the human insulins quickly became widely used. Recently, however, concerns about an increased prevalence of both hypoglycemia and hypoglycemia unawareness when switching patients from animal to human insulin have been reported.[1-6]

This prompted us to review the clinical experience of patients from our office-based diabetes/endocrine practice who had been transferred from animal to human insulin. Our interest focused principally on the clinical efficacy of human insulin versus animal insulin and on any untoward problems, such as hypoglycemia, that may have occurred with the switch.

Charles B. Kahn, MD, is Clinical Professor of Medicine, Brown University, Providence, Rhode Island.

R. Preston Lamberton, MD, is Associate Clinical Professor of Medicine, Brown University, Providence, Rhode Island.

Dennis S. Krauss, MD, is Associate Clinical Professor of Medicine, Brown University, Providence, Rhode Island.

Methods

The charts of 100 patients were selected randomly for a retrospective review. Patients had to have been in our practice long enough to allow 2 years' experience on animal insulin and a like experience after the transfer to human insulin. Data collected from the charts included age, sex, body weight, blood pressure, heart rate, insulin dose in total units of both modified and regular insulin, number of injections per day, blood glucose data (both fasting and postprandial), total glycosylated hemoglobin, and fasting total cholesterol and triglyceride values. Postprandial glucose values were obtained at various times, so the data were summed and averaged for each patient. Ninety-eight percent were Caucasian. Over 90% were on NPH (isophane) insulin as the modified insulin and used Iletin® (Lilly, Indianapolis, IN) mixed beef-pork insulin when on animal insulin and Humulin® when switched to human insulin.

All laboratory tests were performed in our office. Blood glucose and lipid values were measured on the ASTRA-8 (Beckman Instruments, Inc, Brea, CA). Total glycosylated hemoglobins were done by the Coleman Junior II A Linear Absorbance Spectrophotometer (Coleman Instruments, Oak Brook, IL).

Our patients usually had two or three office visits per year. Over 2 years, four or more individual pieces of datum were available for each determination. These data were averaged for each patient for the 2 years on animal insulin and for the 2 years on human insulin, thus allowing a statistical comparison. At each office visit patients were asked about the frequency and severity of insulin reactions. Usually, the number per month was recorded.

Several methods were used to analyze the data. Student's paired t-test was found to be the best method to compare data between the animal and human insulins.

Results

At the time of transfer, 44 patients were younger than 40 years of age. The age of onset of diabetes was below 30 years of age in 53 patients and younger than 40 years of age in an additional 12 patients. These could be considered type I diabetic patients. Table 1 shows the clinical data. After the transfer, body weight data showed a small but significant weight gain (157 ± 41 vs 161 ± 43), systolic and diastolic blood pressure showed a small but significant decrease (131 ± 17 vs 128 ± 15 and 76 ± 6 vs 75 ± 5), respectively, and heart rate did not change.

The analysis of pharmacological data (Table 2) included insulin dosage and number of injections daily. An increase in total dose of both modified

ABBREVIATIONS USED:

DNA: Deoxyribose nucleic acid
NPH: Neutral protamine, Hagedorn

and regular insulin was noted with the switch to human insulin and was statistically significant for the summed total of both types of insulin (51 ± 24 vs 56 ± 27). The average number of daily injections increase slightly but statistically significantly after the transfer (1.5 ± 0.4 vs 1.6 ± 0.5).

Table 3 shows postprandial glucose and glycosylated hemoglobin values. A significant difference in mean postprandial glucose values was found (232 ± 68 vs 207 ± 60) and indicated a decrease in blood glucose when switching from animal to human insulin. This was also reflected in the total glycosylated hemoglobin values (9.8 ± 9 vs 9.6 ± 1). Total glycosylated hemoglobin values are represented as absolute values and percentage above or below the upper limit of normal for our laboratory, which is 8.4%

Data were limited for total cholesterol and triglyceride values. The data were not significantly different between the two insulins, but due to the small numbers and wide scatter of values, further presentation of lipid values is not made.

When transferred to human insulin, 91 patients did not indicate any difference in the frequency of insulin reactions, 6 patients noted a slight increase in the number of reactions, and 3 had fewer reactions. None indicated any change in the severity of reactions or the appearance of reactions without warning (hypoglycemia unawareness).

Table 1. **Clinical Data**

	Average ± Standard Deviation (range)			
Insulin Source	Weight lb.	Heart rate beats/min	Systolic Blood pressure mm HG	Diastolic Blood pressure mm HG
Animal	157 ± 41* (71-302)	74 ± 5 (53-93)	131 ± 17* (100-173)	76 ± 6* (48-100)
Human	161 ± 43* (79-333)	73 ± 4 (64-92)	128 ± 15* (93-168)	75 ± 5* (62-94)

*p ≤ .05

Table 2. **Pharmacological Data**

	Average ± Standard Deviation (range)			
Insulin Source	Modified Insulin dose (units)	Regular Insulin dose (units)	Total Insulin dose (units)	Number of injections daily
Animal	40 ± 17* (14-86)	12 ± 10* (0-53)	51 ± 24* (20-131)	1.5 ± .4* (1-2.5)
Human	42 ± 19* (15-95)	13 ± 12 (0-73)	56 ± 27* (15-168)	1.6 ± .5* (1-3)

*p ≤ .01

Table 3. **Outcome Data**

	Average ± Standard Deviation (range)		
Insulin Source	Postprandial glucose, mg/dl	Absolute value (ghbb)	Percent of control (ghbb)
Animal	232 ± 68 (107-430)	9.8 ± 9* (8-13.3)	117 ± 11* (96-158)
Human	207 ± 60* (84-397)	9.6 ± 1* (7-12.1)	114 ± 13* (84-144)

*p ≤ .03
ghbb = glycohemoglobin

Discussion

A retrospective review of the records of 100 patients transferred from animal-source insulin to human insulin showed that the transfer to human insulin resulted in a decrease of glycosylated hemoglobin and postprandial blood glucose. There were no untoward effects including any indication of frequency or of change in symptoms of hypoglycemia. There was a small increase in total units of insulin used and number of injections each day on human insulin. There was a modest increase in weight; 5% of the patients showed a more than average weight gain. The increase in weight, however, remained significantly greater on human insulin even after these 5% were deleted from the statistical analysis. Weight gain is a common clinical experience. Of note, and unexpected, is a slight but statistically significant lowering of blood pressure. The mechanism for this decrease in blood pressure is unknown.

The improvement in glycemic control with human insulin may have a number of etiologies. The study design does not allow determination of whether the transfer from animal to human insulin is the sole cause of improvement of metabolic control. However, it has been shown that human insulin has a more rapid onset of action that may result in improved postprandial glucose control and lower glycosylated hemoglobin.[7]

In a controlled study[8] comparing postprandial glucose and metabolic

concentration in type I diabetes after subcutaneous injections of human and purified pork insulin, postprandial plasma glucose was lower after human than with pork insulin. In addition, the shorter duration of action of human insulin in comparison to mixed beef-pork insulin may require more individual doses of insulin, as was the case in these patients.

The division of total dose into more than one injection each day can result in a higher dose of insulin being given with less risk of hypoglycemia. Additionally, improvement in glycemic control may result from modifications of other aspects of diabetes treatment, such as increased glucose monitoring, improved patient compliance, better patient or family education, or intensified efforts to improve diabetic control.

The goal of insulin therapy in both type I and type II patients is to ameliorate symptoms of uncontrolled diabetes and prevent acute and chronic complications of diabetes by lowering the blood glucose level toward normal. Although the effect of glycemic control on micro- and macrovascular complication has not been established, available information indicates improvement of diabetes control may be protective against progression of microvascular complications.[9,10]

The only apparent clinically meaningful concern with the use of human insulin identified in the literature is an alleged increased prevalence of hypoglycemic episodes and of hypoglycemia unawareness. This "alarm" was raised by a small group.[3,5] Our clinical experience and the data do not confirm these observations. A few patients indicate an increased number of hypoglycemic events, and a still smaller number noted a reduced likelihood of reactions when transferred to human insulin. More than 90% noted no change in the number of insulin reaction. None of the patients indicated any increase in the severity of or lack of awareness of insulin reactions (hypoglycemia unawareness) when using human insulin. Such has been the experience of others.[11-16] A recent report comparing the counter regulatory hormone response to hypoglycemia showed no difference between porcine and human insulin.[17]

Of note is the carefully designed prospective trial in which intensive, tight control was the objective. Although the frequency of reactions increased in the tight control group, analysis did not indicate a relationship between human insulin use and asymptomatic or symptomatic hypoglycemia.[1]

The goal of insulin therapy in both type I and type II patients is to ameliorate symptoms of uncontrolled diabetes and prevent acute and chronic complications of diabetes by lowering the blood glucose level toward normal.

No other problems were noted in our clinical practice when 100 patient charts were reviewed retrospectively in an office-based practice to evaluate clinical and laboratory parameters before and after transfer to human insulin. The data collected indicated that after transfer to human insulin there was improvement of glycemic control without an increase in adverse events.

Acknowledgment

The authors wish to thank Kathleen Sweet, RN, Jennifer Iovini, and Sally Guertler for their assistance in data collecting and Yvette Mace for manuscript preparation. This study was done under a grant from Eli Lilly Co., Indianapolis, Indiana.

References

1 DCCT Research Group. Epidemiology of Severe Hypoglycemia in the Diabetes Control and Complications Trial. *Am J Med* 90:450-459, 1991.

2 Berger WG, Althuas BU. Reduced awareness of hypoglycemia after changing from porcine to human insulin in IDDM (Letter and Comment). *Diabetes Care* 110:260-261, 1987.

3 Berger W, Keller U, Honegger B, Jaeggi E. Warning symptoms of hypoglycaemia during treatment with human and porcine insulin in diabetes mellitus. *Lancet* 1:1041-1044, 1989.

4 Teuscher A, Berger WG. Awareness of hypoglycemia in diabetes (Letter). *Lancet* 2:919, 1987.

5 Teuscher A, Egger MN. Human insulin hypoglycaemia unawareness (Letter). *Lancet* 1:1072, 1989.

6 Teuscher A, Berger WG. Hypoglycemia unawareness in diabetics transferred from beef/porcine insulin to human insulin. *Lancet* 2:382-385, 1987.

7 Galloway JA, Root MA, Bergstrom R et al. Clinical pharmacologic studies with human insulin (recombinant DNA). *Diabetes Care* 5(Suppl 2):13-22, 1982.

8 Gulan M, Gottesman IS, Zinman MD. Biosynthetic human insulin improves postprandial glucose excursions in type I diabetes. *Ann Intern Med* 107:506-509, 1987.

9 Klein R, Klein BEK, Moss SE, Davis MD, DeMets DL. Glycosylated hemoglobin predicts incidence and progression of diabetic retinopathy. *JAMA* 260:2864-71, 1988.

10 Pirart J. Diabetes mellitus and its degenerative complications: A prospective study of 4,400 patients observed between 1947 and 1973. *Diabetes Care* 2:168-88, 1978.

11 Berger M. Human insulin: Much ado about hypoglycaemia (un)awareness. *Diabetologia* 30:829-833, 1987.

12 Gorden P. Human insulin and hypoglycemia (Correspondence). *N Engl J Med* 322:1007-1008, 1990.

13 Hepburn DA, Eadington DW, et al. Symptomatic awareness of hypoglycemia: Does it change on transfer from animal to human insulin? (Letter). *Diabetic Med* 6:586-590, 1989.

14 Hepburn DA, Frier BM. Symptomatic awareness of hypoglycemia: Does it change on transfer from animal to human insulin? (Letter-Rebuttal). *Diabetic Med* 7:269-270, 1990.

15 Cryer PE. Human insulin and hypoglycemia unawareness (Letter and Comment). *Diabetes Care*. 13:536-538, 1990.

16 Mulhauser I, Heinmann E, et al. Hypoglycemic symptoms and frequency of severe hypoglycemia in patients treated with human and animal insulin preparations. *Diabetes Care*. 14:745-749, 1991.

17 Jones TW, Caprio S. Does insulin species modify counterregulatory hormone response to hypoglycemia? *Diabetes Care* 14:728-731. 1991.

Address correspondence to:
Charles B. Kahn, MD
49 Seekonk Street
Providence, RI 02906

For Lease or Sale

1700 Sq. Ft. Office
Lab & X-Ray
49 Seekonk Street
Providence, RI

Contact:

Harold Horwitz 351-2280
Joseph Lombardozzi 351-2280
Charles Kahn 351-7100

Radon: Health Implications in Rhode Island

Richard V. Morgera, MD

Rhode Island is believed to hold potentially large sources of radon gas in some areas.

Radon is an invisible, odorless, naturally occurring radioactive gas found mostly in ground soil. Its clinical impact results from household exposure to the gas after silent entry into the indoor atmosphere. Radon is found in most parts of the country including Rhode Island, which is felt to hold potentially large sources of this gas in some areas.

Radon itself is the decay product of naturally occurring uranium ore. Although radon is an inert gas, it is not stable. Radon's decay products, referred to as "radon daughters," represent a variety of heavy metals that hold an electrostatic charge and are thus chemically active. Because of this charge, the radon daughters can attach themselves to free-floating particles in the air such as dust and smoke. Upon inhalation, they will adhere to the respiratory mucosa. As the radon daughters themselves decay, they release three types of potentially harmful radioactive particles. Alpha particles have high energy and large size thus they move slowly and produce the greatest tissue damage. Beta particles and gamma rays have greater penetrating power than alpha particles but move through tissue quickly causing less tissue damage and deliver a lower dose of radiation to the exposed area.

Autopsy studies on miners exposed to radioactive ore, as long as 100 years ago, revealed a high incidence of lung cancer.

Richard V. Morgera, MD, is in private practice with Family Medicenter, Middletown, Rhode Island.

Since those first observations, numerous studies have shown an association between radon gas exposure and the subsequent development of bronchogenic carcinoma. Of the lung cancers that develop in miners exposed to high levels of radon, no specific cell type has been noted to predominate in histological studies.[1] There is a definite synergistic carcinogenic effect between radon exposure and cigarette smoking.[2]

Radon originates from the degradation of uranium found naturally in rock and soil.

The development of lung cancer from radon exposure is directly proportional to the level and duration of exposure.[3] The level of radon is best determined by measurement of the gas in a given area. This measurement is expressed as picocuries per liter of air (pCi/L). Since it is actually the degradative products of radon gas that emit the biologically hazardous radiation, it is their energy release that is most important. Working levels (WL) were developed as a way of calculating the amount of radon daughters that miners were exposed to. One WL is the amount of radon degradation products in one liter of air that will result in the emission of 1.3×10^5 Mev of alpha energy from their decay. In a typical household atmosphere 200 pCi/L of radon gas will convert to 1 WL of energy release. Since, as previously stated, the biological impact of radon in the development of lung cancers in humans is proportional not only to the working level of exposure but also the duration, the cumulative exposure then is expressed as working level months (WLM), which relates WL measurements to the amount of time spent in the specific radon exposure environment.

Radon originates from the degradation of uranium ore found naturally in rock and soil. Concentrations are highest in granite, phosphate and shale rock. Granite deposits underlie most of New England including Rhode Island. The Reading Prong is an extensive uranium-bearing granite formation in Pennsylvania on which houses were built. It is in these houses that some of the highest indoor radon concentrations have been recorded. Phosphate rock is prevalent in Florida and, unfortunately, spurred by dramatic population growth over the past decade, many residential projects have been built on reclaimed phosphate-mined soil that releases high levels of radon.

In the soil, radon travels by simple diffusion. The rate of diffusion depends on many variables. Faster diffu-

ABBREVIATIONS USED:

EPA: Environmental Protection Agency
Mev: Million electron volts
pCi: Picocuries
RISE: Rhode Islanders Saving Energy
WL: Working levels
WLM: Working level months

sion occurs in loose or sandy soil while slower movement is noted in dense and wet soils. Environmental factors also affect diffusion rate. A temperature gradient between air and ground soil will speed diffusion via a vacuum effect as warm air rises. This same effect occurs with low atmospheric barometric pressures "pulling" radon out of ground soil.

After diffusion through ground soil, radon enters the indoor atmosphere by penetrating the house foundation via openings or is carried in with well water. Included in these entry portals are sump pump openings, concrete basement floor cracks and joints and french drains. Unfortunately, certain building products also contain radon including granite concrete containing phosphate slag and fly ash and phospho-gypsum wallboard.

In the United States widespread testing of radon levels in homes has not been implemented. The EPA therefore has estimated that as many as 8 million homes have elevated levels of radon. The EPA has set as a national standard the highest acceptable value for annual average radon exposure at 4 pCi/L. This standard was arrived at through evaluation of several studies of radon exposure in miners. This standard does not represent a "safe" level but rather a level above which corrective action is "strongly recommended." A radon level of 4 pCi/L (0.2 WL) correlates with the same health risk as undergoing 400 chest X-rays in a year and the same lung cancer risk for a non-smoker as for a one-half pack-a-day smoker.[4]

In 1988 the EPA undertook a large-scale radon testing program in 17 states. From this study it was found that the average radon level was 1.5 pCi/L but that 20% of homes tested had levels over 4.0 pCi/L.

Radon levels in the home can be determined by use of an activated charcoal monitor. These screening devices are inexpensive, readily available and provide quick, accurate results. Initial levels should be obtained in the basement where reading will be highest in the house. If this initial test result exceeds the EPA recommended level of 4.0 pCi/L, a more long-term test is recommended to determine levels over time and in a variety of atmospheric and weather conditions that may affect diffusion. The most common long-term radon test is the alpha track detector that will give reliable radon concentration measurements over a 3 to 12 month period. Again, if the alpha track level exceeds 4.0 pCi/L, remedial action then should be taken to lower radon levels.

Table 1. **Household Concentrations of Radon**

	RI EPA	RI Volunteer	RISE	National EPA
Number households measured	485	2379	350	11,600
Average radon level (pCi/L)	3.3	5.0	–	1.5
Percent of houses that exceed 4.0 pCi/L	21.4	34.4	31.0	21.0

Several states, including Massachusetts and Connecticut, make it mandatory that the presence of health hazards, such as radon, be disclosed when selling a home.

Elimination of radon from the indoor atmosphere may require multiple corrective measures. These include: 1) closure of all pathways that allow radon gas penetration such as sealing cracks and joints in the concrete foundation and covering exposed earth and sump-pump openings in cellar floors; 2) subslab ventilation systems that will direct the source of radon in the ground soil under and around the basement and exhaust it to the exterior or 3) replacing or sealing building materials that contain radon. More sophisticated and expensive measures can be undertaken but these initial measures will be successful in most situations.

To date, three studies have looked at the radon problem in Rhode Island. Two have revealed that the average indoor radon level in RI exceeds that measured nationally by the EPA. Secondly, there is a significant number of homes in Rhode Island that exceed the EPA standard of 4.0 pCi/L (Table 1).[5] In fact, the RI Department of Health estimates that 80,000 to 130,000 Rhode Island homes exceed this level.

Conclusions

Radon is a significant health hazard causing an estimated 10,000 lung cancer deaths per year from its daily household presence. A significant number of Rhode Island homes exceed the EPA standard of safety. In a recent RISE survey of the general population in Rhode Island, 97% of the 408 households surveyed reported that they had heard of radon and its health implication but only 17% of these same households had ever tested for its presence.[6] Screening tests are simple and inexpensive. If initial levels are high, a subsequent longer term test is recommended and remedial actions taken if these high levels are verified. Most radon-lowering measures are relatively inexpensive and successful. The general population must be urged to test their homes and simple charcoal testers must be made readily available for their use. Several states, including Massachusetts and Connecticut, make it mandatory that the presence of health hazards, such as radon, be disclosed when selling a home.[7] Rhode Island should adopt this law as well.

References

1 Harley N. Potential lung cancer risk from indoor radon exposure. *Cancer Journal for Clinicians* 40:265-275, 1990.

2 Birper R, et al. Radon: counseling patients about risks. *Arch Fam Prac.* 7:711-718, 1990.

[3] Samet J. Radon and lung cancer. *J National Cancer Institute*. 1989 81:745-75.
[4] Radon, A Physician's Guide. AMA. September 1990.
[5] Bela M, et al. Residential indoor air radon levels in Rhode Island: Summary of state experience to date. Rhode Island Department of Health August 1990.
[6] Attitudes towards radon, energy and the environment among Rhode Islanders. RISE. May 1990.
[7] Home selling headaches. *US News and World Report*. September 16, 1991; 62-64.

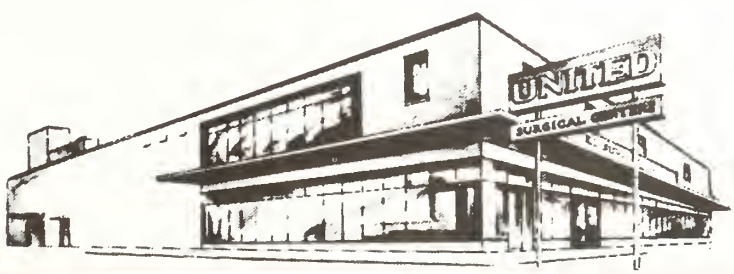
General Source
LaFavore M. *Radon, The Invisible Threat*. Rodale Press, 1987.

Address correspondence to:
Richard V. Morgera, MD
Family Medicenter
Polo Center
700 Aquidneck Avenue
Middletown, RI 02840

333 School Street
Pawtucket
▽
Blackstone Valley Medical Building
▽
Custom-made office
For lease or sale
724-7722

There must be a good reason why we've become the trusted back-up resource for more Rhode Island doctors (and their patients) than anyone else.

UNITED SURGICAL CENTERS
The Professionals in Home Health Care Equipment



We carry just about EVERYTHING for Home Health Care . . . which means, everything a patient or convalescent needs to implement the doctor's treatment directions. For Ostomy and Oxygen needs to Orthopedic Appliances. Wheelchairs. Walkers and Hospital Beds. we're here to serve your patients. Our staff is knowledgeable and dedicated to supplying exactly "what the doctor ordered". We've been doing it dependably for many years.

That's how we've earned the trust of so many doctors.

Medicare and Third Party Claims Accepted and Processed.

380 WARWICK AVE., WARWICK
781-2166

HEALTH BY NUMBERS

Rhode Island
Department of Health
Barbara A. DeBuono, MD, MPH
Director of Health

Decline in Cigarette Smoking Among Rhode Island Women

In 1987, lung cancer deaths exceeded breast cancer deaths as the leading cause of cancer mortality among Rhode Island women for the first time. The lung and bronchus were the primary site of 19% of fatal cancers among women, compared to 17% for the breast and 15% for the colon and rectum.

The mortality rate from women with lung cancer has been increasing rapidly in recent years. The age-adjusted rate from 1983 to 1987 was up 151% from the rate for 1968 to 1972, only 15 years earlier. This compares with a 12% increase among Rhode Island men. During this same period, women's mortality rate for all causes has fallen by 20%, while the individual mortality rates for virtually all other major causes of death have declined by up to 43%. (Heart disease was down 30%; stroke was down 43%; breast cancer was down 3%; and colon cancer was down 21%.)

The leap in lung cancer mortality reflects the increases in cigarette smoking among women that occurred from the 1940s until the release of the Surgeon General's Report on Smoking and Health in 1963 and parallels the experience of men a generation earlier.

At the same time that lung cancer mortality has been increasing, the smoking rate among women has shown a steady decline from the peak in the 1960s. In Rhode Island, the proportion of women who smoke, as determined from health surveys, was 37% lower in 1990 than in 1975 (Figure 1). From 1975 to 1985, the decline in smoking rates among women was slower than the decline among men, and it appeared that at some point the proportion of men who smoke would fall below that for women in Rhode Island. However, the most recent data, for 1990, show the women's rate falling more sharply than before, in parallel with that for men, so that women maintained their differential relative to men.

Smoking rates among women in Rhode Island remain high relative to rates seen in neighboring states and in the rest of the United States (Figure 2). Among all women age 18 and older, a higher percentage in Rhode Island was smokers than in Connecticut or Massachusetts, and Rhode Island's rate was also higher than the median figure for all states. Among younger women, ages 18 to 44, Rhode Island's smoking rate was the highest of all the states.

Smoking patterns seen among Rhode Island women belie several commonly held views concerning the experience of women and anti-smoking efforts. For one, younger women's smoking rates have declined as well as among older women. For women ages 16 to 19 and ages 20 to 24, the decline in proportion smoking from 1975 to 1990 has been 37% and 45%, respectively, as compared to the decline of 37% for all women. Perhaps because young men's rates have declined even more rapidly, the perception is that young women continue to take up smoking at high rates. Women also are thought to be less successful at quitting smoking than men. Again, among women under age 45, quit rates parallel those for men almost exactly (Figure 3). For women ages 45 and above, quit rates fall below those for men, perhaps because these women did not view the health effects of smoking in their mother's generation, among whom smoking rates remained low.

The picture of women and smoking provided by the most recent data available is a picture becoming remarkably similar to that for men. On the negative side, women are now experiencing the health effects of smoking that have been affecting males for more than a generation. On the positive side, younger women are becoming less likely to begin smoking and more likely to quit smoking once they have started. As a result, the smoking rate among women has accelerated its decline, putting the Year 2000 objective of 15% smokers increasingly within reach for Rhode Island's population.

References

Rhode Island Health Interview Surveys, 1975, 1980, 1985, 1990. Rhode Island Department of Health, Providence, RI.

Behavioral Risk Factor Surveillance System, 1990. Centers for Disease Control, Atlanta, GA.

Submitted by the Office of Health Statistics, Jay S. Buechner, PhD, Chief. Health by Numbers *is edited by Jay S. Buechner, PhD, and William J. Waters, Jr, PhD.*

Figure 1. **Percentage of persons age 16 years and older currently smoking cigarettes, by sex, Rhode Island 1975 to 1990**

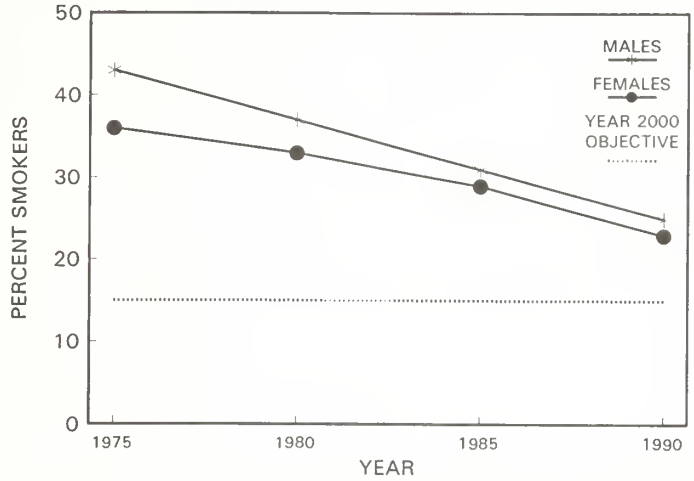


Figure 2. **Percentage of women currently smoking cigarettes, by age group, Rhode Island, Massachusetts, Connecticut and the United States, 1990**

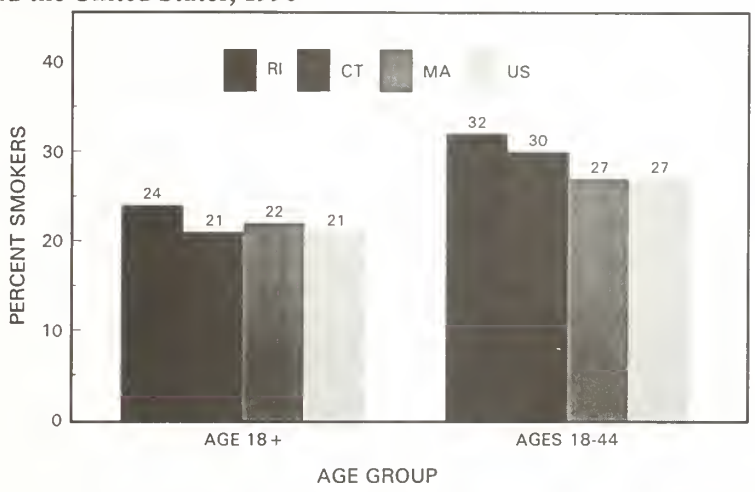
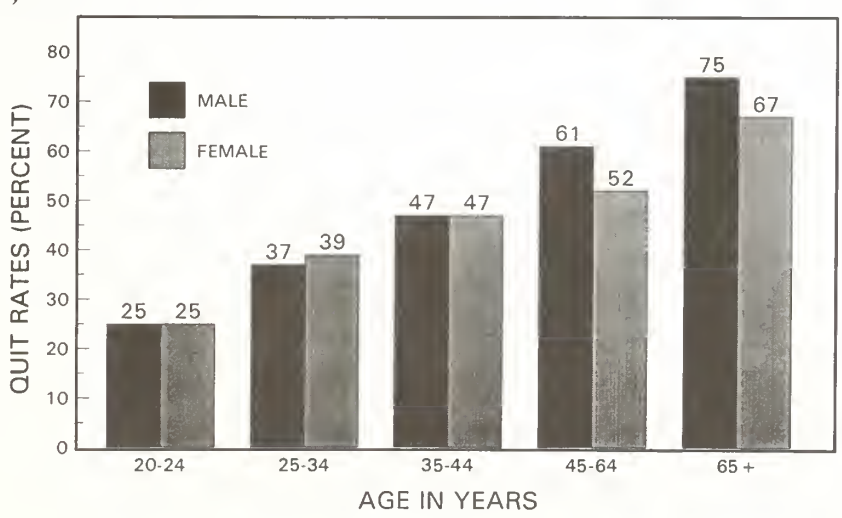


Figure 3. **Percentage of persons ever smoking cigarettes who have quit smoking (quit rate) by age group and sex, Rhode Island, 1990**



Internal Medicine Opportunities - Harvard Community Health Plan of New England (formerly RIGHA) offers excellent opportunities for BC/BE internists to practice in a Rhode Island setting. We currently serve 77,000 members in 5 staff model Health Centers and 1 affiliated Medical Group located in Aquidneck. Our Health Centers provide complete primary and subspecialty care, with on-site laboratory, x-ray and pharmaceutical services. We are affiliated with Brown University and offer academic appointments, teaching appointments and attractive on-call schedules. The salaried position provides an excellent compensation and benefits package.

Please send CVs to:

Patrick Mattingly, MD
President, Medical Director
Harvard Community Health Plan of New England
Coro Center, One Hoppin Street
Providence, RI 02903-4199

Harvard Community Health Plan *of New England*

A Equal Opportunity Employer

Need Information about Businesses? Call the Business *INFOLINE!*

There are over 9 million businesses in the U.S. – and finding information about them can be virtually impossible, especially when you need it *fast.* But now there's a way . . . a revolutionary new service called *Business INFOLINE!* Need to know the address and phone number for "XYZ Company" somewhere in Florida, or the name and phone number of a "Cadillac Dealer" in Palm Beach? Even telephone company directory assistance can't help you in these situations . . . but we can!

For example . . .

"Your BMW breaks down on the interstate, and you need to know if there 's a dealer in the next town."

"An out-of-town company is trying to sell you vinyl siding for your house and you need more information about them – how long the company has been in business, and how many employees they have."

"You're planning a vacation in the Pacific Northwest, and you want to line up things for the kids to do. So you need to find the amusement parks and zoos in Oregon and Washington."

"A friend gave you a tip that "Apex Industries" would be a good investment, but you want to know more. What do they do? What are their approximate annual sales?"

The Business INFOLINE is indispensable for home or office? And the cost is *only* $3.00 for the first minute and $1.50 for each additional minute, conveniently billed to your phone number. The service is available Monday through Friday, 7:00 a.m. to 6:00 p.m., Central Time.

Dial 1-900-896-0000

Ask for Ext. #195

Money-back Guarantee if not satisfied.

A Service of American Business Information • 5711 So. 86th Circle • Omaha, NE 68127

A critical health problem for your patient. A difficult problem for you to treat.

The Miriam Hospital Weight Management Service offers treatment programs addressing all levels of obesity. With over 10 years' experience in obesity treatment and research, our multidisciplinary team provides the resources needed for safe, medically monitored weight loss and for long-term success in maintaining weight loss.

For more information on our programs, or to refer a patient, call:
(401) 861-0870

Portions of our programs may be covered by health insurance.

The Miriam Hospital Weight Management Service
Division of Behavioral Medicine
An affiliate of the Brown University Medical School

Impartial Medical Evaluation

Henry M. Litchman, MD

Any physician who performs third-party assessments should be thorough, keep good records, document findings quantitatively wherever possible and exercise reasonable care with the patient.

Duties and Responsibilities

When in the course of an individual's medical management the legal interest of a third party is involved, an impartial evaluation can be demanded. Failure to respond to this demand, in many cases, can lead to discontinuance of benefits. The purpose of this evaluation is limited to assess the individual's impairment. There is no attempt at treatment, and there is no physician-patient relationship established. It is well established in law that since there is no relationship, there can be no malpractice, and the doctor's only duty to the patient is to conduct the examination in a manner not to cause harm to the person being examined. Very often, and sometimes at the request of the third party, there is no disclosure of medical findings or opinions related to the history and physical examination to the person being examined. The impartial evaluation may be the first encounter a patient has with a second physician in the course of that particular illness or injury, and if the physician feels ethically bound to offer some medical advice, one is obligated to exercise the same degree of care as if a physician-patient relationship existed.

To satisfy existing legal and ethical principles, it is wise for the physician to indicate to the patient that the examination is independent rather than adversary and limited in scope and who is to receive the report. Since the examination was performed for the third party, the information is usually considered confidential, but ethically if a discovery is made that would measurably affect the future course of the patient's condition, either the patient's own physician should be contacted or the patient advised to discuss the disclosed matter with his or her own physician.

Physicians who perform impartial examinations are not without liability as previously mentioned. Physical injury caused by negligence during an examination, though rare, is the most common. Financial injury can be claimed. A negligent examination leading to an erroneous diagnosis and loss of job or intentional submission of a false report also may be claimed. A third cause of claims is libel. Labeling a patient as a malingerer without sufficient proof can be an irresponsible action. The physician may also be liable to the third party on the basis that financial injury resulted from a negligent assessment.

Any physician who performs third-party assessments should be thorough, keep good records, document findings quantitatively wherever possible and exercise reasonable care with the patient as if there indeed was a physician-patient relationship. Courteous and ethical interaction not only will make the evaluation more meaningful but will aid in preventing unpleasant consequences from this medical activity.

The Purpose of the Evaluation

It is the interest of the third party to be aware of the diagnosis of the patient. With a definite diagnosis and a knowledge of the natural history of similar patients with the same problem some idea of the prognosis for recovery can be determined. It is the first purpose of the evaluation to establish the diagnosis by a detailed history, physical examination and review of any diagnostic studies that have been performed in the course of the illness or injury. Most often, this information is not provided to the examiner. In many instances, lay administrators have believed this information would prejudice the examiner's opin-

Henry M. Litchman, MD, is Clinical Professor of Orthopedic Surgery, Brown University, Providence, Rhode Island, and Director, Division of Orthopedic Surgery, The Miriam Hospital, Providence, Rhode Island.

ABBREVIATIONS USED:

AMA: American Medical Association

ion. On the contrary, this information is essential to a proper evaluation. In order to fit all the pieces of information together into a coherent whole, the negative as well as the positive findings must be studied. Following diagnosis, causal relationship should be established.

Disability is defined as a "non-medical" term. It relates to the alterations of an individual's capacity to meet personal, social or occupational demands.

When an end stage of the person's disease or injury has been achieved, the second purpose of the evaluation is addressed. This is to determine the impairment in function that has resulted. Impairment is a "medical" term that describes an alteration in health status. It is generally measured in terms of "functional loss of, loss of use of, or derangement of any body part, system or function" of the injured part or organ system. No system of evaluation will ever be perfect. Not all cases can be analyzed by the same criteria. Accepting this fact, we can and do accept an approach that will fit the maximum number of circumstances and this is the basis for the "Guides to the Evaluation of Permanent Impairment" published by the American Medical Association, now in its third edition. This system is based on a few simple principles. The first is that the body is divided into basic units. For the musculoskeletal system these are the upper extremity, the lower extremity, the spine and the pelvis. Each unit can be subdivided into sections which in turn are further subdivided by joints and digits. The anatomical subdivisions each have a function which can be described by their range of motion. Each anatomical structure is assigned a value. Absence of that particular part is equated with loss of the entire value. Residual parts are assigned a value somewhat less. Based on ankylosis of a joint in functional position a certain value is given with lesser values for less favorable positions. Restrictions of ranges of motion of joints are likewise assigned values based on percentage of the normal range being present. Each joint has a relative value considering its importance to the particular unit of which it is a part.

Another principle in this system is that impairment cannot be greater than 100%. Since the addition of multiple impairments could mathematically exceed 100%, a mathematical manipulation is done with the combined values chart.

In the extremity, the main function is related to mobility and the subsequent ability of the distal portion of the extremity to perform function based on motion, strength, and sensation. The AMA system can measure this very well. In the axial skeleton the problem of measuring function is more complex. It is doubtful that motion of the spine is well correlated with loss of function. In addition it is difficult to measure, even with inclinometer techniques, and is poorly reproducible both inter- and intra-observer. In the latest addition of the AMA Guide, diagnosis related factors and musculoskeletal/neurological factors that require physiologic measurements are included. This is very limited and does not include variables such as torque (force) generation or velocity. It is interesting to note that diagnostically specific categories were not included in considering the extremities except for neurological deficits of root and peripheral nerves and alterations in the vascular supply. This method seems inadequate with our present knowledge of functional assessment of the axial skeleton.

Disability is defined as a "non-medical " term. It relates to the alterations of an individual's capacity to meet personal, social or occupational demands. It is the difference between capacity and requirements. If requirements are low, an impairment is not necessarily disabling. "Handicap" is another concept that requires definition. Under the provisions of federal law, an individual is considered handicapped if there exists an impairment that substantially limits one or more life activities, including work. By this definition, which is too broad, almost anyone who has an impairment would be considered "handicapped." A more practical definition regards the individual as having an obstacle to functional activity which has to be compensated in some way to overcome this impairment. Examples include assistive devices, environmental modification and/or modification of tasks or activities. If there are no modifications that allow the individual to accomplish the necessary task, then that individual is also disabled.

The American Medical Association takes the position that disability determination is a "non-medical activity" and that the physician's role is that of producing a medical evaluation in terms of impairment. Employability is determined , according to AMA standards, by the employer who defines the job demands and conditions of employment and matches this with the capacity, with or without assistive devices or modifications, as defined by the physician.

. . . an individual is considered handicapped if there exists an impairment that substantially limits one or more life activities, including work.

As with disability, employability has both a medical and administrative component. The AMA gives the responsibility to management to specifically assess performance capability. When the employee appears to or claims incapability, an impartial evaluation is required to determine if this incapability is related to a medical condition. Secondly, the impairment has to be expressed in functional terms. Thirdly, the job requirements must also be in functional terms. In these instances, the first task is to perform, or have available, a job analysis. This establishes the performance expectations. From this, the physician determines what kinds of information are

needed to assess the individual's capability with regard to expected physical demands. Very often medical documentation by the treating physician is inadequate to define any discrepancies. This type of evaluation should be performed by a physician with experience in occupational medicine who can better interpret the demands of a job task, design a protocol of determining the worker's capabilities and advise the employer if there is a mismatch. This is a more impartial way of making a determination. Management is not impartial and most often does not have the skill to assess performance capability. This will be a better way to prevent performance failure, reinjury, and prolonged disability. It appears illogical for physicians to delegate the responsibility of disability and employability status to the "non-medical" administrators.

Reports

The ultimate purpose of an Impartial Medical Evaluation is to facilitate the third parties' desire to achieve a rapid resolution of the case. This can only be achieved if the necessary information is in the report. A complete report is also beneficial to the physician since there will be fewer inquiries which are time-consuming and costly and there will be less likelihood of being called to an administrative hearing.

To ensure that no omissions are made, it is wise to follow a standard protocol. Occasionally some agencies requiring reports will ask that certain items be deleted, such as need for vocational rehabilitation or employability.

When recording findings, standard techniques and nomenclature should be used in order to standardize reproducibility between examiners and comprehension by lay readers. When rating impairments, discrepancies between examiners will be matters of facts rather than opinions. In the interpretation of results of diagnostic procedures there is an element of opinion and the interpretation of such results is more prone to discrepancies. It is to be kept in mind that positive tests studies should be correlated with clinical findings and should not be heavily weighted, otherwise they may lead to a false positive diagnosis and prognosis. A good protocol should include a narrative history of the present illness. It should specifically relate the onset and course, previous findings, treatments and responses. The past medical history should include previous hospitalizations, medications, allergies and unrelated medical problems. A physical examination report should include positive findings and specific negative findings to ensure the reader that these elements were not overlooked. One should report the interpretation of X-rays taken at the time of the examination and a review of outside studies, when available. A summary statement should be made giving the diagnosis, stating the degree of confidence that this diagnosis had based on a comparison of subjective complaints with objective findings. A prognosis can be offered if the expected natural history of the illness or injury can be determined with a high degree of certainty. This would include an expected date of full or partial recovery or the fact that an end-point had been reached. The answer to these questions may relate to the present treatment, its adequacy, the necessity for further studies in order to establish the diagnosis or prognosis and the need for surgery in order to resolve the medical problem.

Employability is determined, according to AMA standards, by the employer who defines the job demands and conditions of employment and matches this with the capacity, with or without assistive devices or modifications, as defined by the physician.

The determination of causal relationship also should be addressed. By definition causation implies that an alleged factor, such as an occupational injury, did cause a particular impairment. When more than one factor could contribute to an impairment it may be necessary for the physician to apportion the degree to which non-occupational factors have contributed to the impairment. In writing reports, the possibility that events are involved is meaningless. Probability is the only expression that has legal weight. What we understand as a possibility is the likelihood of less than 50% whereas probability is used to imply a likelihood of greater than 50%. Often this is expressed as "within reasonable medical certainty" that two events are related as to cause and effect.

Another concept often of importance in report writing is the question of aggravation of a previous condition or the fact that a previous condition may be contributing to the persistent or increasing impairment the patient exhibits. An aggravation, in order to have legal significance, must be substantial and permanent. It is necessary to state clearly that any temporary setbacks by a secondary causation have ceased to exist and the patient has returned to the status related to the initial causative event.

The rating of impairment is based on the facts summarized in the report. If all the facts are stated anyone with the knowledge of the rating system should be able to calculate the impairment and come to the same conclusion as to the loss of, or loss of use of, or derangement of any body part, system or function. The physician, however, must state whether this impairment is temporary or permanent. Permanent implies that the condition is static or stabilized and is not likely to improve with further medical treatment.

In some instances disfigurement is an issue with regard to third party liability. By this we imply an altered or abnormal appearance. There are no standards in the medical literature to rate this category; however, the physician can comment on the physical characteristics of the alteration in terms of color, shape, and structure, and where known, its effect on the patient with regard to social and psychologi-

cal alterations in behavior or lifestyle.

Disability, as we have previously suggested, is more an administrative determination implying the diminished capacity, based on the impairment of an individual to meet personal, social or occupational demands. In a comprehensive, impartial medical evaluation the physician can summarize the results of data from the supportive health care team with regard to impairment in these specific areas. Assessment of the effect of impairment on the activities of daily living can be obtained. A job analysis with its physical demands can be graded and results of tests of physical function can be analyzed and graded on a similar scale. By this means, discrepancies between tested ability and job requirements can be identified and a conclusion drawn with respect to the person's capacity to meet the demands of a particular job.

The physician is in the best position to correlate these findings since by training and experience the physician understands best the nature of the physiological functions and their alteration by illness or injury. To give up the responsibility for assessing disability to the administrative adjudicators prevents them from exercising their responsibility since they need all available medical information and analysis to do their job.

In summary, although no system rating is perfect we do have means available to analyze extremity function which are well standardized and accepted. Trunk function systems now in existence are not physiologically based and require improvement. The physician should accept responsibility to quantitate data which will objectify disability determination and employability. Impartial medical evaluation is a specialized medical endeavor that requires the skill of a physician who is experienced in the injuries and illnesses of the body system involved in the impairment and is knowledgeable in the process of evaluation.

Address correspondence to:
Henry M. Litchman, MD
The Miriam Hospital
164 Summit Avenue
Providence, RI 02906

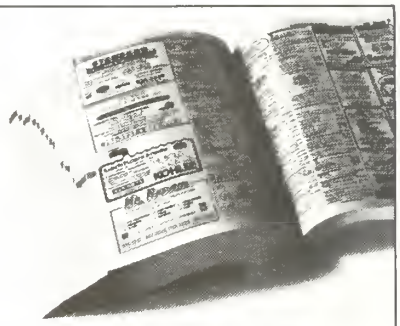
RHODE ISLAND COMPUTERIZED IMAGING, INC.

Cat Scan Facility
401•751•1110

weekdays
7 am - 5 pm

- Evening appointments for contrast studies
- Medicare, Ocean State
  Rhode Island Blue Cross/Blue Shield approved
- Board Certified Radiologist

Located in: Atwood Medical Center
Suite LL3
1524 Atwood Avenue
Johnston, RI 02919



You Shouldn't Choose A Debt Collection Service The Same Way You Choose Your Plumber.

I.C. System is the collection service that has been endorsed by over 1,100 trade and professional associations.

Our methods are highly effective, our newly expanded collection programs are the most advanced in the country.

Next time skip the Yellow Pages and call I.C. System—direct.

1-800-325-6884

An Approved Membership Service of the Rhode Island Medical Society

I.C. SYSTEM

©1991 I.C. System, Inc.

NURSING PLACEMENT
HOME CARE INC.

"The 1st Choice in Certified Home Health Agencies"

We Are Proud To Announce:

NURSING PLACEMENT HOME CARE, INC.,
a **MEDICARE** and **MEDICAID CERTIFIED AGENCY.**

NPHC, the only letters that define Quality and Dependable Home Health Care in RI. Your patients deserve a choice and **NPHC** can offer them that – with a complete range of care options from Home Health Aides to Registered Nurses and all therapies.

We have provided your hospitals and private patients with quality care for 15 years and are now certified to serve all homebound patients in Rhode Island.

- RN assessments
- 24 hr. supervision
- RN
- HHA
- PT
- OT
- Speech
- MSW
- IV Therapy
- Pediatrics

"For Home Care You Can Rely On"

NPHC

Please call 453-4474
1-800-287-2940

YOCON®
YOHIMBINE HCl

Description: Yohimbine is a 3a-15a-20B-17a-hydroxy Yohimbine-16a-carboxylic acid methyl ester. The alkaloid is found in Rubaceae and related trees. Also in Rauwolfia Serpentina (L) Benth. Yohimbine is an indolalkylamine alkaloid with chemical similarity to reserpine. It is a crystalline powder, odorless. Each compressed tablet contains (1/12 gr.) 5.4 mg of Yohimbine Hydrochloride.

Action: Yohimbine blocks presynaptic alpha-2 adrenergic receptors. Its action on peripheral blood vessels resembles that of reserpine, though it is weaker and of short duration. Yohimbine's peripheral autonomic nervous system effect is to increase parasympathetic (cholinergic) and decrease sympathetic (adrenergic) activity. It is to be noted that in male sexual performance, erection is linked to cholinergic activity and to alpha-2 adrenergic blockade which may theoretically result in increased penile inflow, decreased penile outflow or both.

Yohimbine exerts a stimulating action on the mood and may increase anxiety. Such actions have not been adequately studied or related to dosage although they appear to require high doses of the drug. Yohimbine has a mild anti-diuretic action, probably via stimulation of hypothalmic centers and release of posterior pituitary hormone

Reportedly, Yohimbine exerts no significant influence on cardiac stimulation and other effects mediated by B-adrenergic receptors, its effect on blood pressure, if any, would be to lower it; however no adequate studies are at hand to quantitate this effect in terms of Yohimbine dosage.

Indications: Yocon® is indicated as a sympathicolytic and mydriatric. It may have activity as an aphrodisiac.

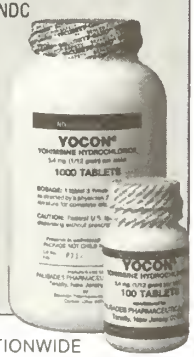
Contraindications: Renal diseases, and patient's sensitive to the drug. In view of the limited and inadequate information at hand, no precise tabulation can be offered of additional contraindications.

Warning: Generally, this drug is not proposed for use in females and certainly must not be used during pregnancy. Neither is this drug proposed for use in pediatric, geriatric or cardio-renal patients with gastric or duodenal ulcer history. Nor should it be used in conjunction with mood-modifying drugs such as antidepressants, or in psychiatric patients in general.

Adverse Reactions: Yohimbine readily penetrates the (CNS) and produces a complex pattern of responses in lower doses than required to produce peripheral a-adrenergic blockade. These include, anti-diuresis, a general picture of central excitation including elevation of blood pressure and heart rate, increased motor activity, irritability and tremor. Sweating, nausea and vomiting are common after parenteral administration of the drug.[1,2] Also dizziness, headache, skin flushing reported when used orally.[1,3]

Dosage and Administration: Experimental dosage reported in treatment of erectile impotence.[1,3,4] 1 tablet (5.4 mg) 3 times a day, to adult males taken orally. Occasional side effects reported with this dosage are nausea, dizziness or nervousness. In the event of side effects dosage to be reduced to ½ tablet 3 times a day, followed by gradual increases to 1 tablet 3 times a day. Reported therapy not more than 10 weeks.[3]

How Supplied: Oral tablets of Yocon® 1/12 gr. 5.4 mg in bottles of 100's NDC 53159-001-01 and 1000's NDC 53159-001-10.



References:

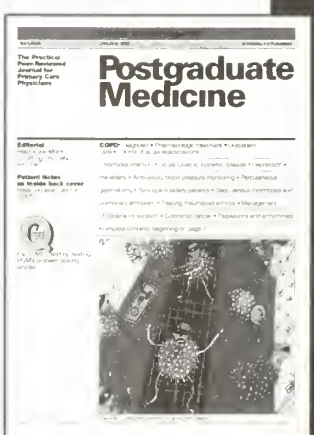
1. A. Morales et al., New England Journal of Medicine: 1221. November 12, 1981.
2. Goodman, Gilman — The Pharmacological basis of Therapeutics 6th ed., p. 176-188. McMillan December Rev. 1/85.
3. Weekly Urological Clinical letter, 27:2, July 4, 1983.
4. A. Morales et al., The Journal of Urology 128: 45-47, 1982.

Rev. 1/85

AVAILABLE AT PHARMACIES NATIONWIDE

PALISADES PHARMACEUTICALS, INC.
219 County Road
Tenafly, New Jersey 07670
(201) 569-8502
1-800-237-9083

US THEM



WHEN YOU NEED TIME ON YOUR SIDE, THE CHOICE IS CLEAR.

NO CLINICAL CLUTTER— PGM ARTICLES ARE CLEAR, CONCISE, WELL ILLUSTRATED, AND PRACTICAL.

Postgraduate Medicine

THE RHODE ISLAND MEDICAL JOURNAL

The Official Organ of the Rhode Island Medical Society
Issued Monthly under the direction of the Publication Committee

VOLUME 1
NUMBER 1

PROVIDENCE, R. I., JANUARY, 1917

PER YEAR $2.00
SINGLE COPY, 25 CENTS

THE RHODE ISLAND MEDICAL JOURNAL HERITAGE

Ninety Years Ago
(June, 1902)

The Providence health department issues the following notices regarding scarlet fever and diphtheria: For a variety of logistical reasons, the use of the throat culture method for determining the time of release in cases of diphtheria will now be abandoned. Hereafter, when a case of diphtheria is identified, the house will be placarded and the children in the family will be excluded from school and kept home. (*For readers who have never seen (or prescribed) quarantine placards, the RI Medical Society still exhibits a few in its library room. – Ed.*) Adults, however, will not be excluded from work. Isolation will be maintained until 10 days after disappearance of the exudate. In cases of scarlet fever, the period of isolation will be four weeks and until desquamation shall have ceased.

RFT Rogers, MD, uses his presidential address to describe the pauper labor of Providence (ie, its physicians). After much analysis of various economic forces upon the practicing physician, particularly those of a new phenomenon called malpractice law suits, he concludes with the following observation as to what is needed: It is the unification of the profession, organization of its branches, systematic missionary work among its members, free discussion of the evils and abuses which exist, careful study of those which are in the profession itself, and eternal antagonism to those outside its ranks, and above all concerted action. This will not occur in our day, but we may be the pioneers of the work, and our children's children will reap the benefits. What we can do is to make our organization, this Association, such a power in this city that thinking people will respect its wishes, politicians fear its influence, corporations ask its advice and shyster doctors dread its disapproval. When every reputable physician belongs to this Association, irrespective of school or creed, the only requirement that he be a legalized practitioner, an educated physician, an honest man, then cliques and crowds will disappear and mutual admiration societies adjourn *sine die*, then the questions affecting the profession will be discussed and decided by the profession, then those who indulge in unworthy practices and harmful to the public, will be called to task.

SA Welch, MD, discusses the diagnosis and treatment of diseases of the gallbladder. The author describes in great detail the methods of examining the right upper abdominal quadrant. Auscultation, he notes, is of little value, but he describes cases "where the stones can be heard to grate together." The use of the X-ray, he states, has usually been found unsatisfactory since stones of cholesterine will not appear. With jaundice, he observes, there is absence of blood coagulability, a moderate diminution of the hemoglobin and a degeneration of the corpuscles. Under treatment, the author talks first about relief of pain and he suggests morphine, Also, oral chloroform water, or valerian in hot water may be tried. A cold water enema may provide some limited relief. He advises against surgery during the acute attack. When obesity or diabetes mellitus are concurrently present, operations are not very successful.

This issue of the *Journal* contains a lengthy letter from Charles V. Chapin, MD, entitled Letter from Havana. It begins with the following statement: Whoever during our New England winter needs a change of scene will find that a trip to Havana offers all that can be desired. Having noted the unique tourist attractions of Havana, Chapin then devotes the remainder of the letter to a sober and scholarly discussion of the sanitary history of this Cuban city. Yellow fever, he notes, has existed continuously in Havana for 150 years. He then summarizes the conclusion of a recent army commission headed by Surgeon Walter Reed. (1) It was proved that yellow fever is transmitted by the bites of a mosquito (*stegomyia fasciata*) as was suggested by Dr Charles Finlay many years before, and just as malaria is transmitted by anopheles. (2) Yellow fever is not transmitted by fomites and is not caused by filth. Chapin then describes the public health measures undertaken by the local sanitary officer, a Major Gorgas, including campaigns to exterminate mosquitoes and their breeding sites. Since these measures were vigorously pursued, he states, Havana has been free of yellow fever for the first time in 150 years. Furthermore, the systematic draining of swamps in the

suburbs has exterminated the anopheles in many sections of the city and has cut down the death rate from malaria in half. Strict methods of isolation coupled with extensive vaccination have also reduced smallpox from an average death list of 600 to none at all for 18 months. He closes his informative letter with the following statement: This city of Havana is healthy today because the health officials have studied the cause of certain diseases and have fought each on a special line. It is a triumph for the scientific physician, not for the engineer.

The proceedings of the Rhode Island Medical Society are summarized. Note is made that the library (housed in the Providence Public Library) increased its resources by 453 volumes including many gifts of rare texts from Drs Noyes and Chapin. The Society's cash balance was $3,915.07

Fifty Years Ago
(June, 1942)

The lead article in this issue of the *Journal* is the Presidential Address by FV Hussey, MD, this being the 130th year in the history of the Society. The address is a sobering reflection upon American history and the periodic sacrifices required particularly during intervals of war. He concludes: "We are asked now to give no more than our forefathers gave to put us where we are. If we love our way of life, if we love our children, should we not do as much? Let us forget our differences... and all turn to help and perpetuate the most glorious way of life this world has ever known."

Frank B. Cutts, MD, offers a review article on arthritis, discussing particularly the diagnostic and therapeutic components of rheumatoid, degenerative and gouty arthritis.

BE Clarke, MD, offers a scholarly article on the history of the microscope, ascribing the first recognition of the magnifying effects of curved glass to a 13th century English monk named Roger Bason. Raphael's portrait of Pope Leo X (1513) shows clearly, the Pope holding a hand lens. Other portraits of that century also display the use of primitive spectacles. Numerous scientists used lenses to magnify small objects but it was Leeuwenhoek's modifications that led to the fundamental design of the current microscope. He was also the first, according to Clark, to cut cross-sections using a razor and to employ transmitted light. His first major publication (to the Royal Society of London) was in 1673. Clarke brings the history to the latter decades of the nineteenth century, noting in passing that such American personages as Cotton Mather, Thomas Prince (pastor of Old South Church, Boston) and Oliver Wendell Holmes possessed personal microscopes and made numerous botanical and entomological observations with it.

This issue of the *Journal* lists the Rhode Island physicians in active military service (79 in number) with another 30 recently commissioned but not as yet activated.

Twenty-Five Years Ago
(May, 1967)

In the lead article, Mario Tami, MD, presents a case report of an 18-year-old woman with a supravalvular aortic stenosis caused by a congenital and stretching across the origin of the aorta. The coarctation was surgically opened longitudinally and a prosthesis inserted. The patient recovered and is now asymptomatic. The author notes that supravalvular lesions account for less than 6% of cases of aortic stenosis. He also comments on the possible association of this lesion with certain chromosomal abnormalities.

Nathan Sonkin, MD, discusses the office management of bleeding peptic ulcer and illustrates his recommendation with a case history of a 52-year-old male with a bleeding duodenal ulcer.

M Finkelstein, PhD, provides the readers with a biography of the eminent scientist Bernhard Zondek, MD (1891-1966) and his notable contributions to the field of reproductive endocrinology.

Harry Darrah, MD, retiring president of the Rhode Island Medical Society, offers a retrospective commentary on the image of the doctor, community action and Blue Shield.

Mrs. JY Barrett, as president of the Society's Woman's Auxiliary recounts the numerous community actions and health program contributions of this organization.

Editorials in this issue of the *Journal* address such important problems as the brain drain from overseas and American responsibilities; the clinical laboratory load and whether automation represents a solution; new clues to the nature of diabetes mellitus; surgery in alcoholic pancreatitis; and whether or not a new medication called methadone represents a breakthrough in the treatment of chemical dependency.

LAW OFFICES of
WILLIAM G. GRANDE

160 Plainfield Street • Providence, Rhode Island 02909-3744

Information on a one-day mutual consent divorce in the Dominican Republic is available upon request

•

Wills • Bankruptcy

•

Victim of crime cases (State pays the fee)

•

Personal injury claims

•

Divorce • Custody • Support

•

Free consultation • General Practitioner

(401) 944-6430

Rx C3: Coughs, Colds, Flu...

NDC 0372-0048-16 ONE PINT (473.2 ml.)

S-T FORTE™

SUGAR-FREE© ALCOHOL-FREE

(Revised Formula 1-92)

Each 5ml. contains:

HYDROCODONE BITARTRATE U.S.P. .....2.50 mg.
CHLORPHENIRAMINE MALEATE U.S.P. .....2.0 mg.

CIII

Antitussive Antihistamine

CAUTION: Federal law prohibits dispensing without a prescription.

Does not contain: sugar, alcohol, dyes, saccharin, sorbitol, decongestants, mannitol, or xylitol.

Approved for payment by Medical Assistance.

Oral Rx where permitted by State Law.

1 (800) 638-SCOT or (401) 942-8555

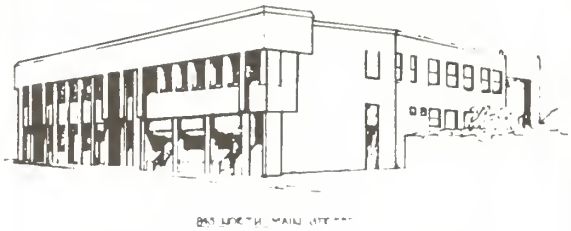
™ *Trade Mark since 1956*

SCOT-TUSSIN

PHARMACAL CO., INC.
CRANSTON, RI 02920-0217 (USA)

®T.M. U.S. Patent Office Reg. #657-674 Printed 3/92

CONDOMINIUMS
FOR SALE OR LEASE

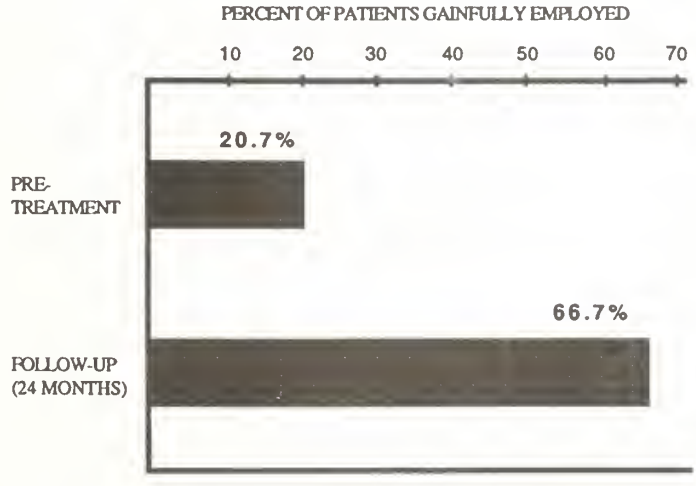


845 NORTH MAIN STREET
PROVIDENCE, RI

- Professional Office and Retail Space
- Convenient Access to I-95
- Minutes from downtown Providence, the Hospitals and Universities
- Ample On-Site Parking

CONTACT: CINDY MORSE, CCIM
PETER M. SCOTTI & ASSOCIATES
60 Ship Street, Providence, RI 02903
CCIM 401-421-8888

"CHRONIC PAIN DOESN'T HAVE TO MEAN CHRONIC DISABILITY FOR YOUR PATIENTS..."



The Chronic Pain Treatment Program
(401) 751-9150

Institute for Behavioral Medicine
120 Wayland Avenue
Providence, Rhode Island 02906-4318

CARE plants the most wonderful seeds on earth.

Seeds of self-sufficiency that help starving people become healthy, productive people. And we do it village by village by village. Please help us turn cries for help into the laughter of hope.

1-800-521-CARE

There's more to Portable X-Ray Service than X-Rays.

Yes, our main business is to provide you with fast, efficient, diagnostic X-Ray services, but we have much more to offer . . . including a staff of people who really care.

- Diagnostic X-Ray Services
- EKG
- Holter-Monitoring*
- Ultrasound Services*
- Same day reporting
- 24 Hour Service
- Seven days a week

*by appointment only

We service the entire Greater Rhode Island area:

- Nursing and Convalescent Homes
- Shut-ins and Private Home Patients
- Post Surgical Patients

PORTABLE X-RAY SERVICE

OF RHODE ISLAND

Certified by the R.I. Department of Health. Reimbursement provided by Medicare, R.I. Blue Shield and Medical Assistance.

100 Highland Avenue Providence, R.I. 331-3996	120 Dudley Street Providence, R.I. 331-3996	154 Waterman Street Providence, R.I. 273-0450	38 Hamlet Avenue Woonsocket, R.I. 766-4224

Call for Papers

1993 International Conference on Physician Health
January 28-31, 1993. Scottsdale, Arizona

Facing Issues, Seeking Solutions, Advocating Help

The 1993 International Conference on Physician Health, co-sponsored by the American Medical Association, the Federation of State Medical Boards, the Canadian Medical Association, and the Federation of Medical Licensing Authorities of Canada is scheduled for January 28-31, 1993, at the Marriott Mountain Shadows Resort in Scottsdale, Arizona. The conference will provide a forum for practitioners and researchers to present recent findings and innovative treatment and educational programs in the area of physician health. This conference will address a range of issues relative to physicians, including AIDS, the HIV positive physician, problems related to aging, health promotion among physicians, mental illness, physical disability, and substance abuse among physicians. Possible topics for presentation include: incidence of health problems among physicians, the presentation of health problems by physicians, their treatment, the impact of disorders on physician's family and practice, medical-legal implications of various disorders, and the impact of these disorders on hospital administrations. *Abstracts which address issues related to these topics (i.e., diagnosis, treatment, rehabilitation),but not dealing specifically with physicians are also welcome.*

Three types of presentations regarding these physician health issues are invited:

- **Poster Presentations**

Written presentations of data-based research, epidemiological research, or descriptive papers regarding treatment and educational programs.

- **Paper Sessions**

Oral presentation of scientific, data-based findings relative to topic of physician health.

- **Workshops**

Training or instructional presentations, designed to improve specific skill levels of persons who work in the area of physician health.

Abstracts for poster presentations and paper sessions should contain an introductory statement on the significance of subject matter. Description of methods, results, and conclusions should follow the introductory statement.

Abstracts for workshops should contain information on the program's intended audience, goals, teaching strategies, and materials. Evaluation data should be summarized.

Abstract may not exceed *200* words. Any abstracts exceeding that length will be rejected. Abstracts should be typed, double spaced, and mailed (not faxed). Four copies of the abstract should be sent, along with one self-addressed, stamped envelope. All submissions must list the primary and secondary authors and their professional affiliations. Telephone number and address of primary author must also be included.

Paper and Workshop submissions should indicate any audiovisual equipment that is needed.

Submissions *must* be received by June 15, 1992.

Abstracts will be submitted for blind review. Abstracts will be judged on their applicability to the conference topic area and their scientific merit. The decisions of the blind reviewers will be communicated to the abstract's primary author by August 15, 1992.

All persons who have an abstract accepted for presentation at the conference are expected to register for the conference. We are unable to reduce registration fee for presenters, nor are we able to provide any financial support for presenters. All persons who attend the conference will be responsible for their own transportation and hotel expenses, as well as making all reservations for same.

Send all materials to:

Patrick W. McGuffin, PhD, Department of Mental Health, American Medical Association, 515 North State Street, Chicago, IL 60610.

American Medical Association

Physicians dedicated to the health of America

INFORMATION FOR AUTHORS

Manuscripts: Manuscripts will be accepted for consideration with the understanding that they are original contributions, have never been published or submitted elsewhere, and are submitted only to the *Rhode Island Medicine*.

Specifications: Manuscripts must be original typed copy (not all capitals) on 8-1/2 x 11 inch firm typewritten paper, double-spaced throughout (including title page, text, acknowledgments, and references) with margins of at least one inch and using but one side of each page. Tables, charts, and legends should be submitted separately from the text, and referred to by number (ie, Fig. 1) within the text. Subheadings must be inserted at reasonable intervals to break the typographic monotony of the text. Pages must be numbered consecutively. Italics and boldface print are never used except as subheadings.

Abbreviations: *Rhode Island Medicine* attempts to avoid the use of jargon and abbreviations. All abbreviations, especially of laboratory and diagnostic procedures, must be identified in the text.

Title Page: All manuscripts must include a title page which provides the following information: (1) a concise and informative title; (2) the name of the author or authors with their highest academic degree (ie, MD, PhD); (3) a concise biographical description for each author which includes specialty, practice location, academic appointment, and primary hospital affiliation; (4) mailing address and office telephone of principal author; (5) mailing address of author responsible for correspondence or reprint requests; (6) source of support if applicable.

Illustrations: Authors are urged to use the services of professional illustrators and photographers. Drawings and charts should always be done in black ink on white paper. Clear, black and white 5x 7 glossy photographs should be submitted, and such illustrations numbered consecutively and their positions indicated in the text. Original magnifications should be noted. Illustrations defaced by handwriting or excessive handling will not be accepted. The figure number, indication of the top, and the name of the author must be attached to the back of each illustration. Legends for illustrations should be typewritten on a single list, with the numbers corresponding to those on photographs and drawings. Recognizable photographs of patients are to be appropriately masked and must carry with them written permission for publication.

Special arrangements must be made with the editors for excessive numbers of illustrations. Color plates are not acceptable.

Identification of Patients: Names, initials should not be used. Use of numbers is a preferable form of identification.

Reprints: Because of cost considerations, reprints are not provided routinely to the author(s). Reprints may be ordered separately (100 copies minimum order) and printing costs will be charged to the author(s).

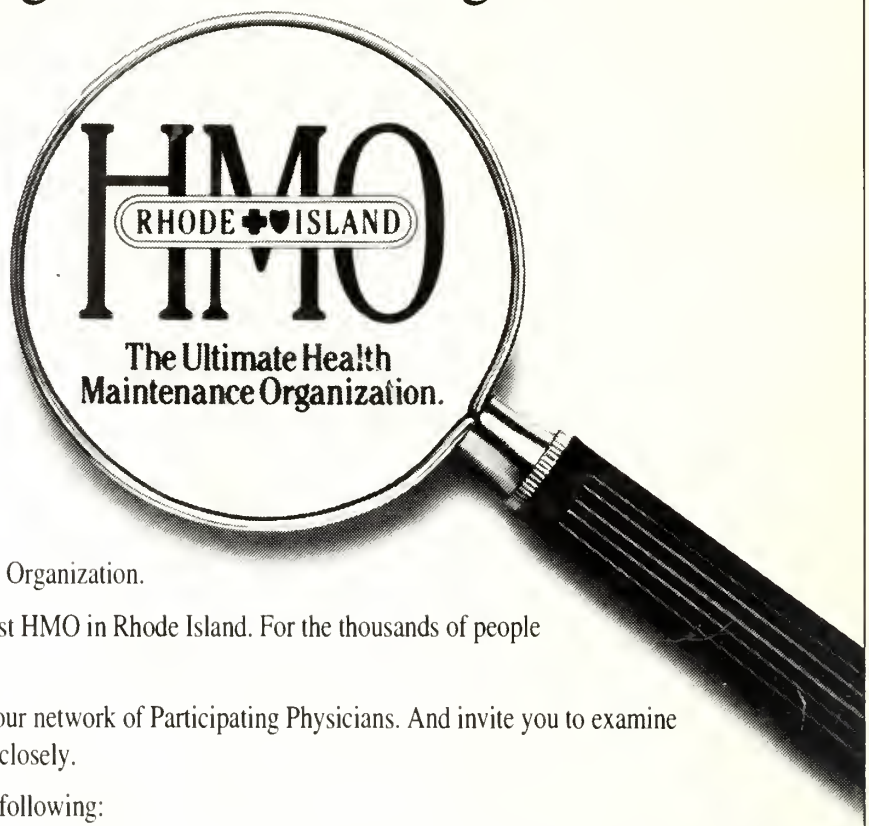
Responsibility: Manuscripts are subject to editorial revisions as deemed necessary by the editors and such modifications will be undertaken so as to bring them into conformity with the style of *Rhode Island Medicine*, which is in compliance with the editorial standards of the AMA. However, neither the editors, nor the publishers, nor the Rhode Island Medical Society will accept responsibility for statements made or opinions expressed by any contributors in any article or feature published in the pages of *Rhode Island Medicine.*

Permission: When material is reproduced from other sources, full credit must be given both to the author and publisher of these sources. Where work is reported from a governmental service or institution, clearance by the appropriate authority must accompany the manuscript.

References: To conserve space and expense, references should be limited to those essential to the subject. The editor reserves the right to reduce the number when it is deemed necessary. The references must be double-spaced and numbered as they appear consecutively in the text, with their positions clearly indicated in the text. All references must be checked to assure complete accuracy. Each journal reference must include the full name of the author(s); complete title of paper; name of publication; volume number; issue number; first and last page of paper; and date (year, month, and day as indicated). Each book reference must include the full name of author(s), editor(s), or both, with initials; title of book; edition; publisher; location; year of publication, volume (if given); and page number. If the reference is to a chapter within a book, the author of the chapter, if different than the author of the book, and the title of the chapter (if any) must be provided.

Correspondence: All correspondence relating to publication should be addressed to: Managing Editor, *Rhode Island Medicine*, 106 Francis Street, Providence, RI 02903.

Before you join an HMO...
Make sure you give ours a thorough examination.



First, check out our tagline.
The Ultimate Health Maintenance Organization.

Very simply, we feel we're the best HMO in Rhode Island. For the thousands of people enrolled in our plan. And for you.

That's why we'd like you to join our network of Participating Physicians. And invite you to examine HMO Rhode Island closely. *Very* closely.

You'll find only we offer you the following:

- ✔ Competitive fee schedules. We offer higher office visit allowances than other major plans. And payment terms for our Primary Care Physicians are available in either capitated or fee-for-service arrangements.
- ✔ Responsive provider relations. Including easy access to both our Medical Director and Provider Relations Staff.
- ✔ Minimal paperwork. No administrative hassles.
- ✔ Service that will more than satisfy you. When we surveyed HMO Rhode Island physicians, an overwhelming number responded as being *very* satisfied with the service they receive from us.
- ✔ An open-door policy when it comes to decisions that affect the future of HMO Rhode Island.
- ✔ Plus, an emphasis on preventive care that puts the focus on you. As an HMO Rhode Island Primary Care Physician, you provide the guidance for your patient in all healthcare decisions.

Look interesting? Let **Physician Recruitment Manager, Carin Cookman** fill you in on the details. When it comes to all HMO Rhode Island has to offer, *seeing is believing.*

HMO
RHODE ISLAND

Call today: 274-6674 or 1-800-528-4141.